

Genetic Analysis of Brain Images from 21,000 People: The ENIGMA Project

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on behalf of the ENIGMA Consortium²*

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Introduction: What is the ENIGMA Project?

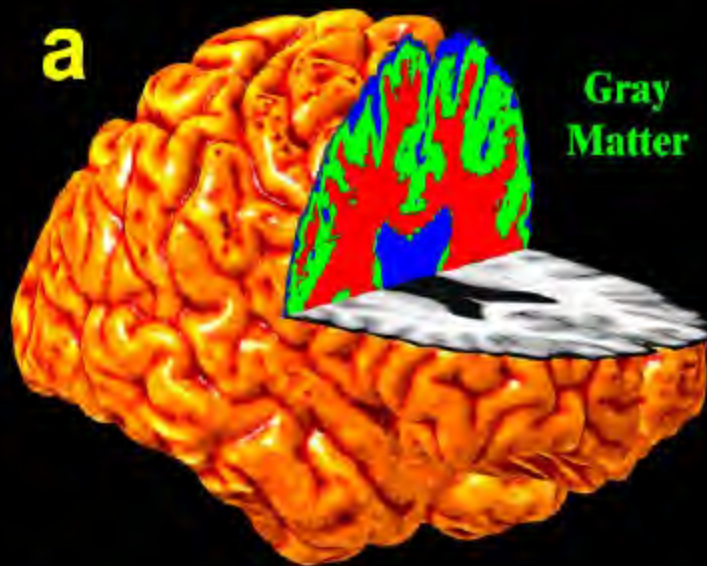
- Worldwide Consortium – we **relate human brain images to genome-wide scans** (>500,000 common variants in your DNA)
- **Discover genetic variants that affect brain** / may also affect disease risk
- Enabled **largest brain imaging studies ever performed** (*Nature Genetics*, Apr 15 2012; 21,151 subjects, now increasing)
 - 207 co-authors, 125 institutions, >500,000 SNPs, range of brain measures (massive global collaboration; “Crowd-sourcing”)
 - Founded 2009 by triumvirate of imaging genetics labs: Thompson (UCLA), Wright/Martin (Queensland), Franke (Netherlands), many more PIs & their teams run Working Groups
 - Working Groups assess different brain measures – ENIGMA2 (morphometry), ENIGMA-DTI, ENIGMA-PIB, ENIGMA-Mouse, ENIGMA-PGC, Case-Control Working Groups

Why screen 21,000 brain images?

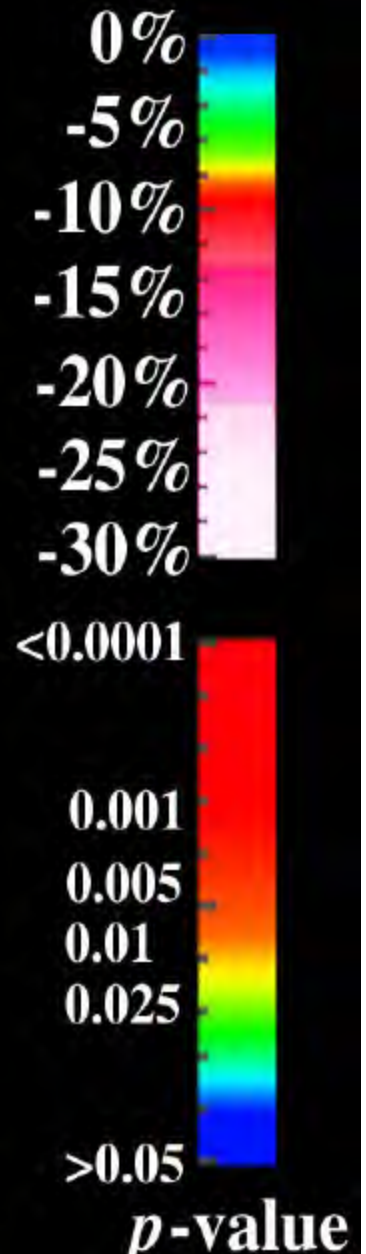
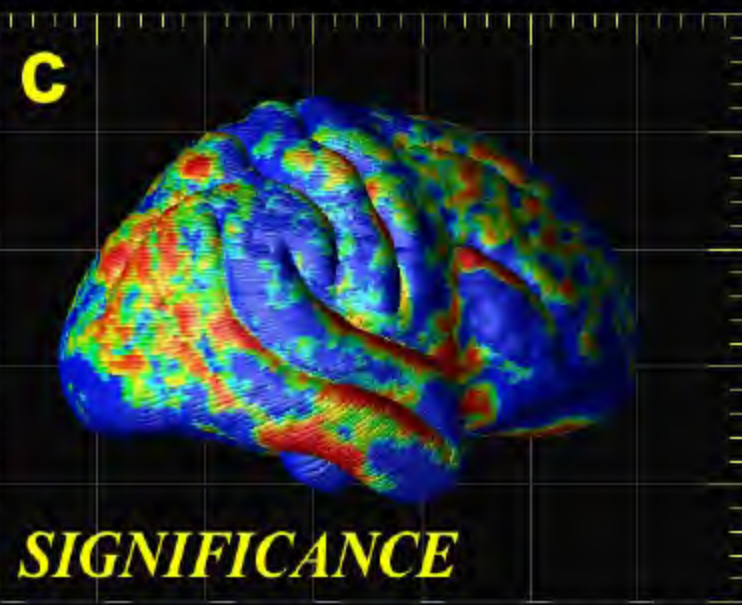
- Amass a sample so vast that we can see how **single-letter changes in your DNA** affect the brain, in the midst of all the other factors that affect your brain (age, education, abused drugs, alcohol, body mass index, ..)
- Do epidemiology with images (exercise, diet, medication)
- Discover genes that:
 - promote brain degeneration / risk for disease, affect brain wiring and organization (new leads in autism, Alzheimer's disease)
 - help estimate our **personal risk** of mental decline
 - **genetic profiling** can empower drug trials (we do this now)

Discover **new drug targets**

What factors harm the brain? 1. Diseases, such as **Alzheimer's** – several commonly carried genes boost our risk for this (*ApoE4*: 3x; *CLU*, *CR1*, *PICALM*: 10-20% more risk each)

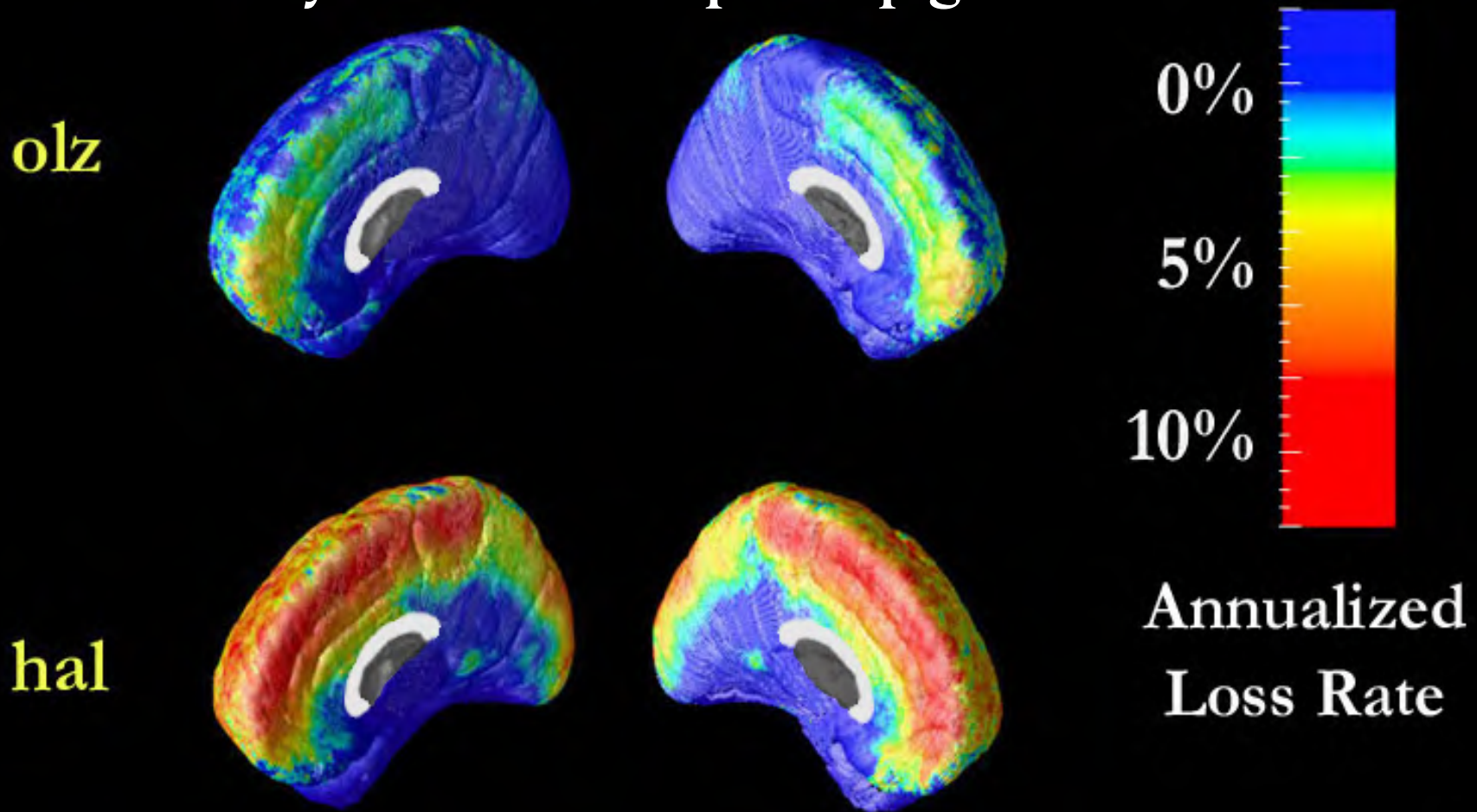


Braak Stage B

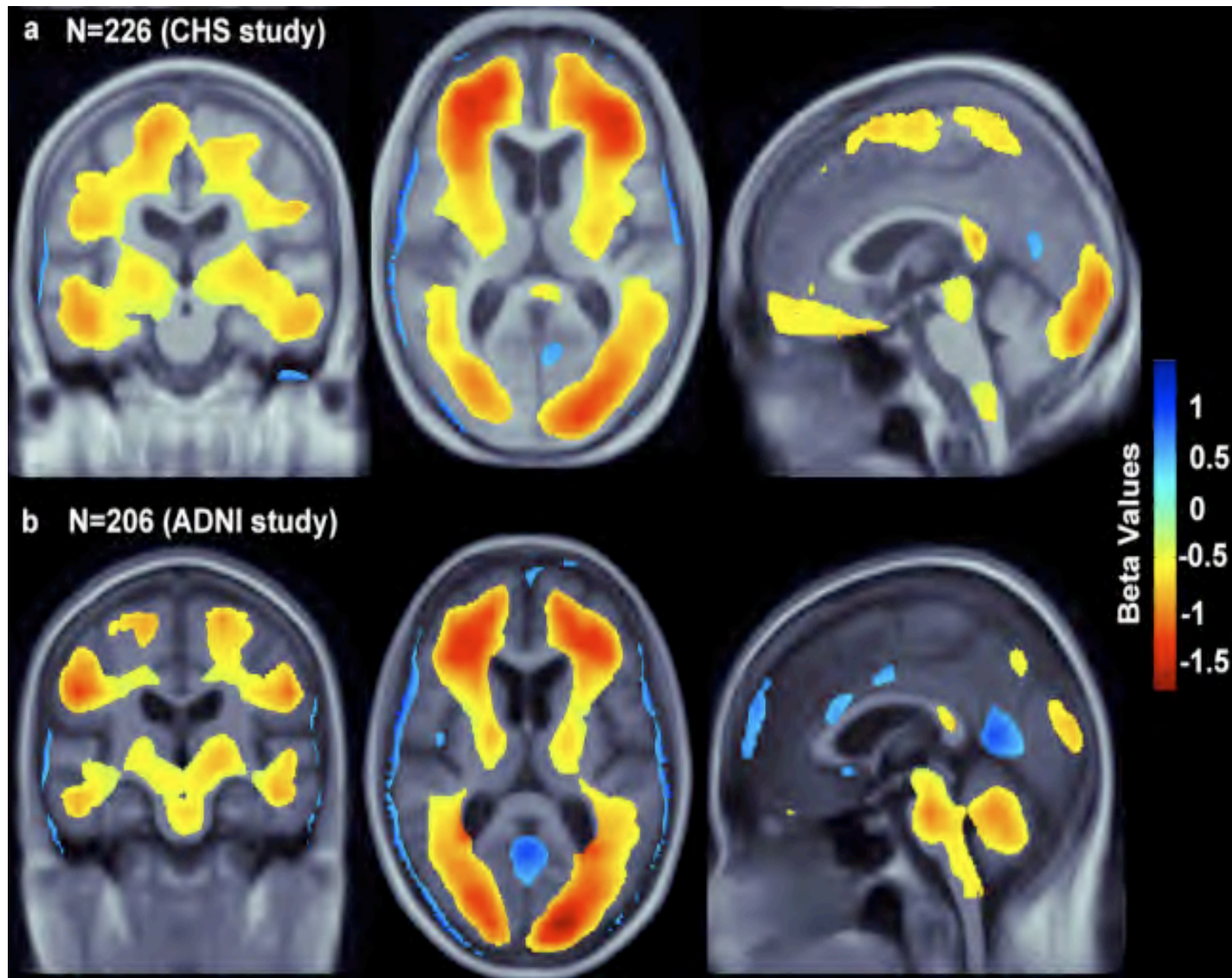




Imaging can pick up very subtle modulatory effects -
Olanzapine Slows Gray Matter Loss;
Imaging Reveals Differences;
maybe it can also pick up gene effects

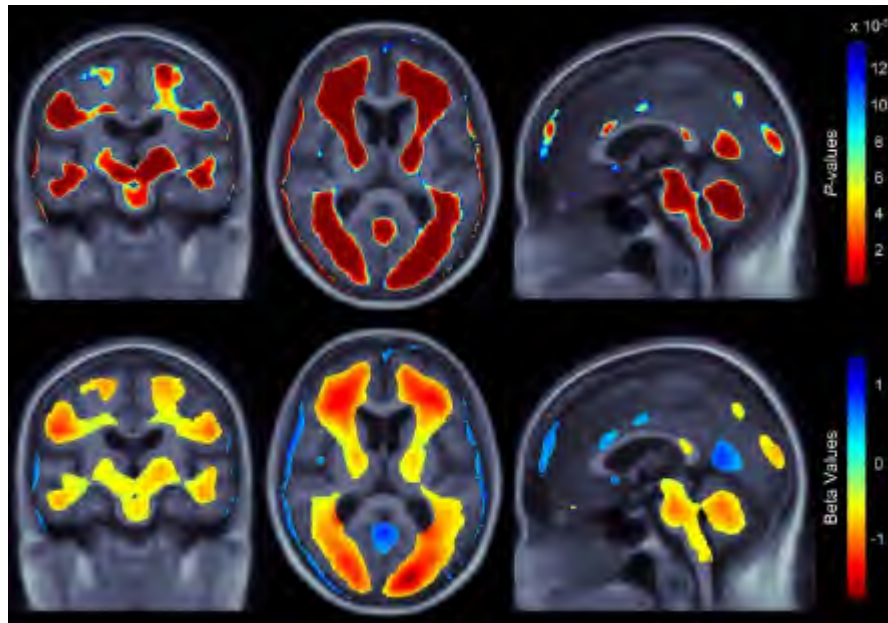


**‘Obese’ People have 8% more brain atrophy locally (N=432 MRI scans).
Maps show % tissue deficit per unit gain in body mass index (BMI)**



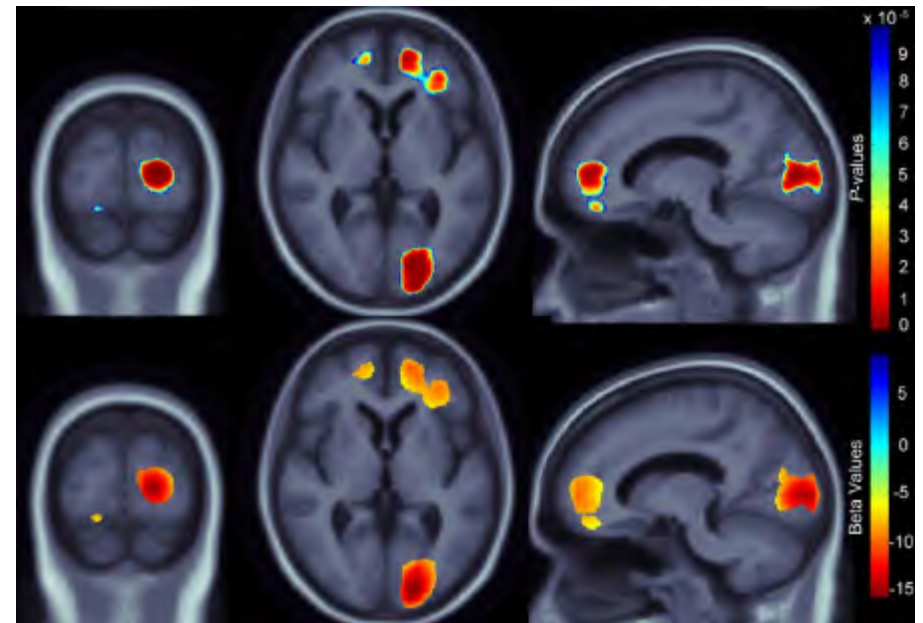
¹Raji et al. Brain Structure and Obesity. *Human Brain Mapping*, Aug. 2009.

Geneticists discovered an “obesity susceptibility gene” (*FTO*) – surprisingly, we were able to pick up the effect of this common variant in brain images (Ho PNAS 2010)



BMI

(N=206 healthy elderly; corrected for multiple comparisons)



***FTO* association**

(N=206 healthy elderly; corrected for multiple comparisons)

Obesity Risk Gene Carriers have Greater Brain Atrophy

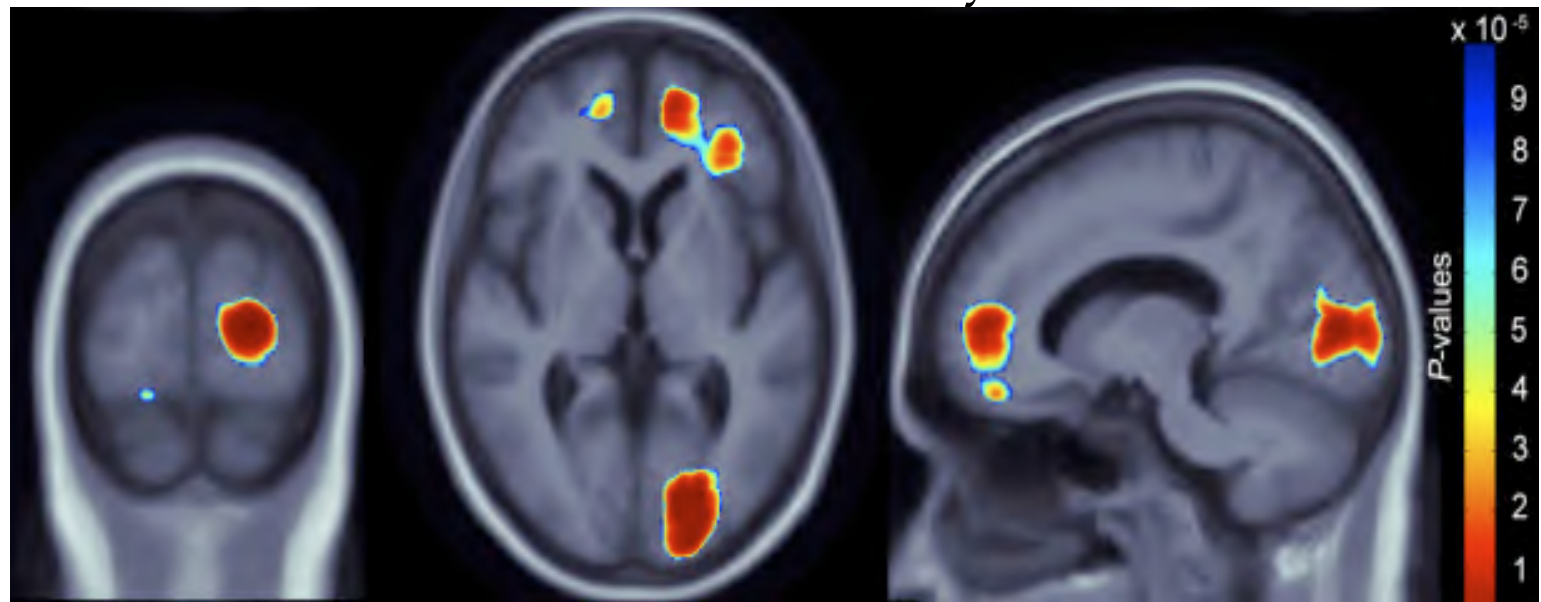
46% of Western Europeans carry at least one adverse allele at this obesity risk locus, in *FTO* gene; for each 'bad' allele:

gain 3 lbs, 1 / 2 inch waist circumference, crave ~200 more calories/day

They have a regional ~10% frontal lobe, ~15% occipital lobe deficit locally – regions with atrophy in people with higher BMI.

May be direct effect on brain, or mediated by BMI, or both

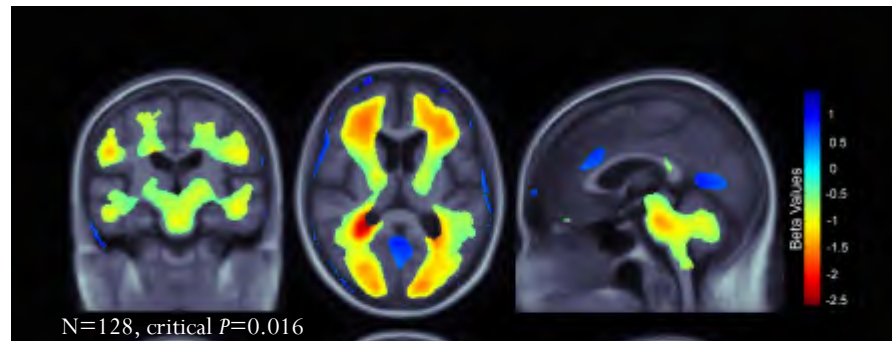
Significance
Maps in
N=206
normal
subjects



April J. Ho^{1*}, Jason L. Stein^{1*}, Xue Hua PhD¹, Suh Lee¹, Derrek P. Hibar¹, Alex D. Leow MD PhD^{1,2}, Ivo D. Dinov PhD¹, Arthur W. Toga PhD¹, Andrew J. Saykin PsyD³, Li Shen PhD³, Tatiana Foroud PhD⁴, Nathan Pankratz⁴, Matthew J. Huentelman PhD⁵, David W. Craig PhD⁵, Jill D. Gerber⁵, April N. Allen⁵, Jason J. Corneveaux⁵, Dietrich A. Stephan⁶, Bryan M. DeChairo PhD⁷, Steven G. Potkin MD⁸, Clifford R. Jack Jr MD⁹, Michael W. Weiner MD^{10,11}, Cyrus A. Raji PhD^{12,13}, Oscar L. Lopez MD¹⁷, James T. Becker PhD¹⁴⁻¹⁶, Owen T. Carmichael PhD¹⁸, Charles S. DeCarli MD¹⁹, Paul M. Thompson PhD^{1,*}, and the ADNI (2010). **Commonly carried allele within *FTO*, an obesity-associated gene, relates to accelerated brain degeneration in the elderly, PNAS 2010.**

Depending on your *FTO* genotype, BMI may affect you in a different way

1 or 2 risk alleles



2 risk alleles



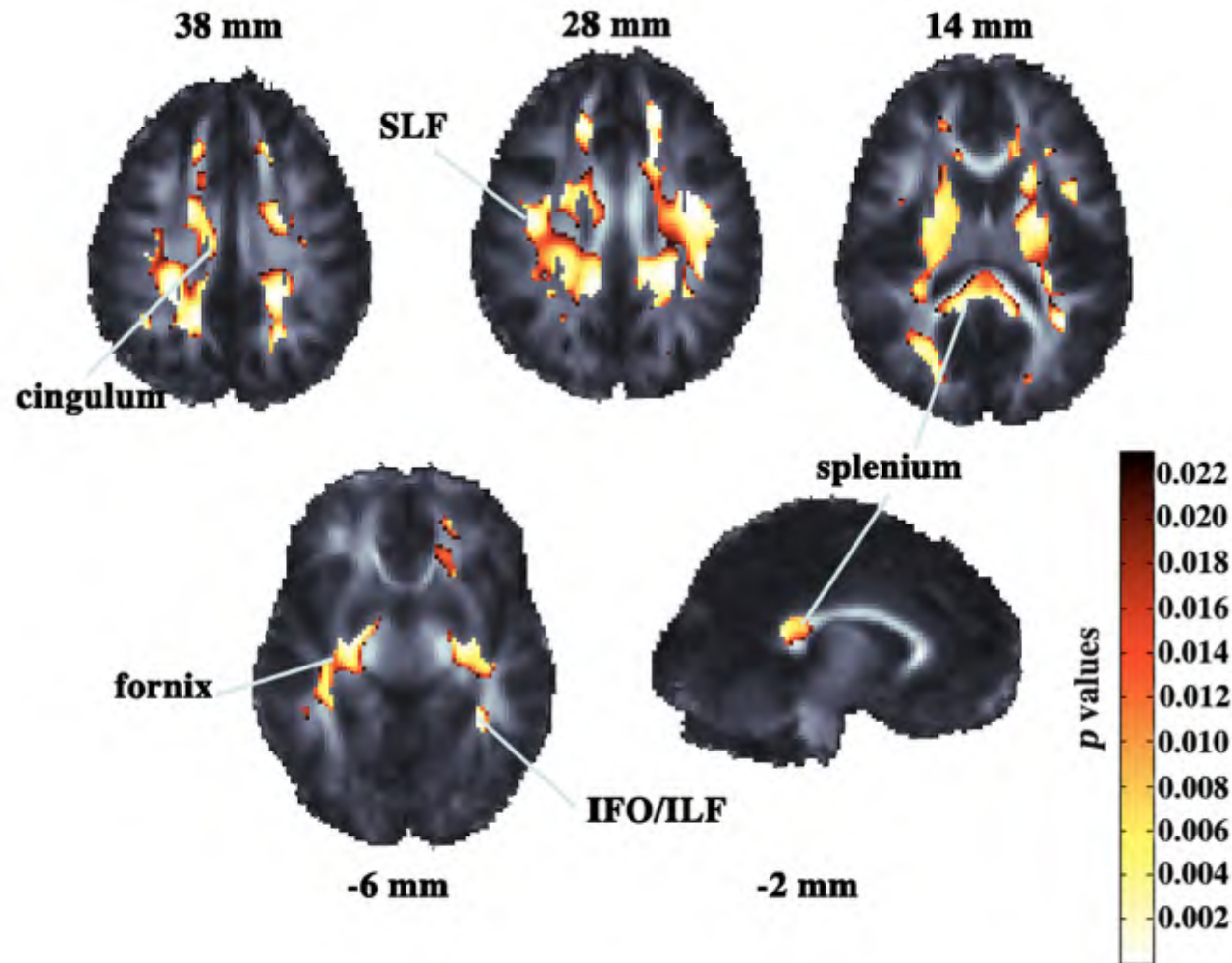
1 risk allele



*Does not pass FDR
at 5% in non-carriers (N=78)



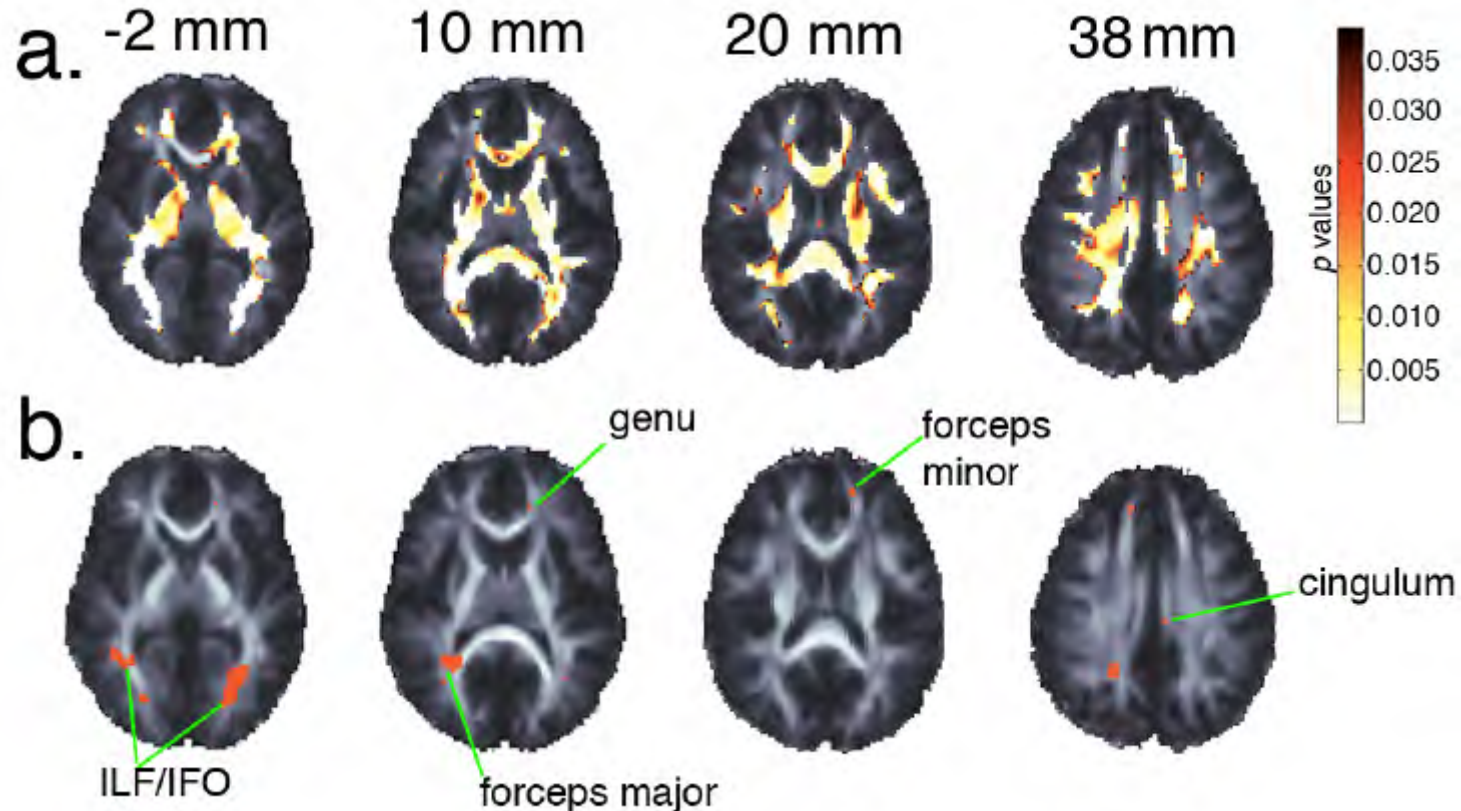
Alzheimer's risk gene carriers (*CLU*-C) have lower fiber integrity even when young (N=398), 50 years before disease typically hits [News covered in 20 countries]



Voxels where *CLU* allele C (at rs11136000) is associated with lower FA after adjusting for age, sex, and kinship in 398 young adults (68 T/T; 220 C/T; 110 C/C). FDR critical $p = 0.023$. Left hem. on Right

Braskie et al., Journal of Neuroscience, May 4 2011

Effect is even stronger for carriers of a schizophrenia risk gene variant, $trkA-T$ (N=391 people)

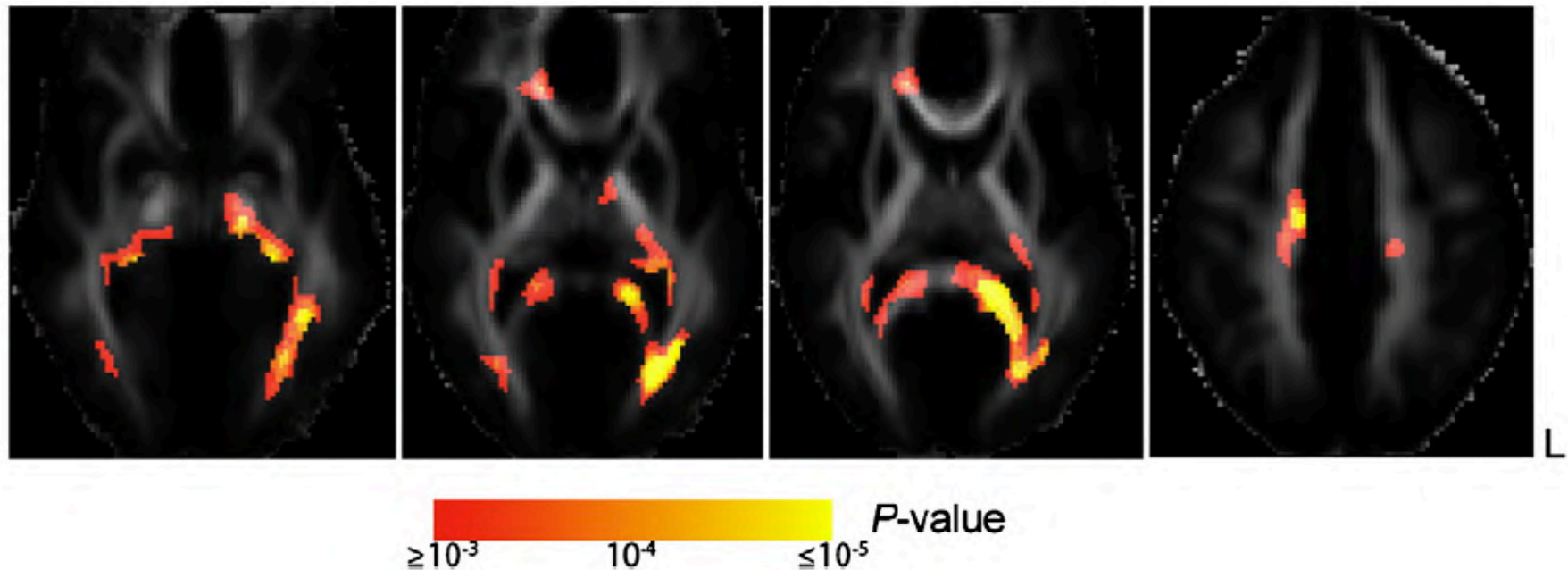


a. p values indicate where $NTRK1$ allele T carriers (at rs6336) have lower FA after adjusting for age, sex, and kinship in 391 young adults (31 T+; 360 T-).

FDR critical $p = 0.038$.

b. Voxels that replicate in 2 independent halves of the sample (FDR-corrected). Left is on Right.

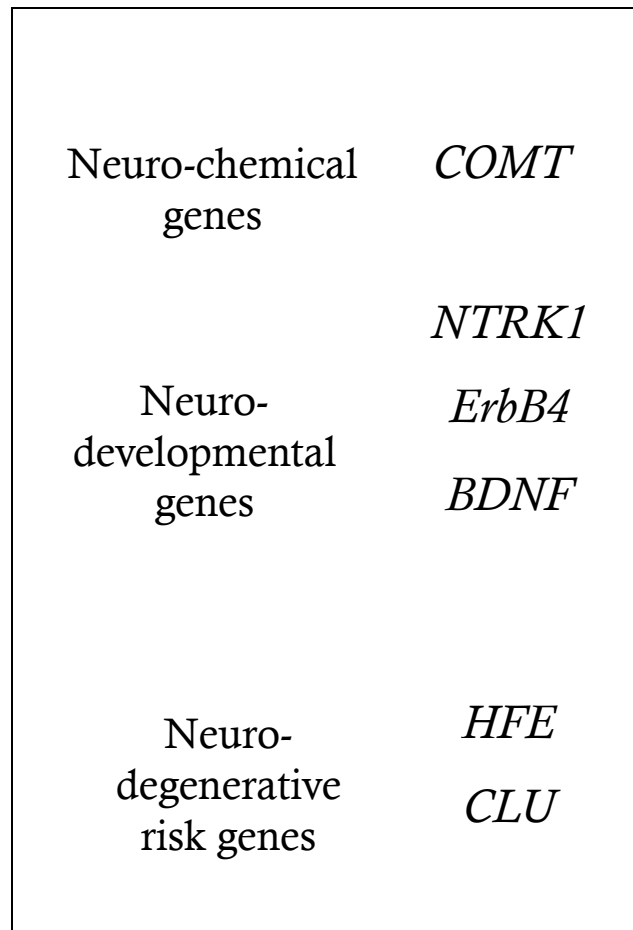
...also found for *BDNF* gene (N=455 people). This is a well-known growth factor gene. Has been associated with working memory.



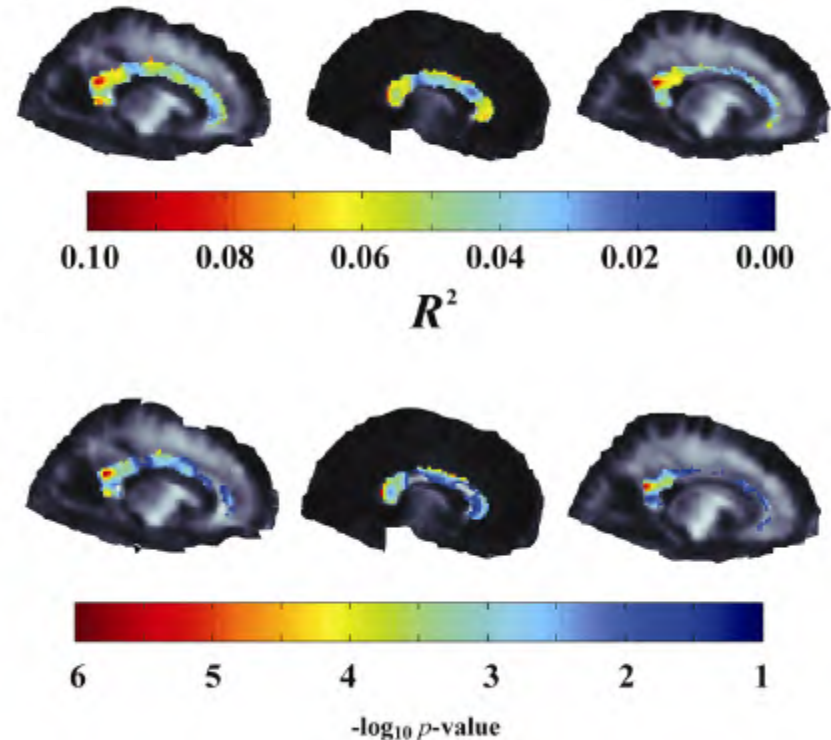
Can we use these discoveries to **develop a genetic test to help predict your brain integrity?**

To some extent yes. Use a **polygenic prediction model** based on all these SNPs.

We developed a polygenic test that can **predict a small proportion of the variance in brain integrity** (7 SNPs) and rate of brain loss (empower drug trials)



A



A significant fraction of variability in white matter structure of the corpus callosum (measured with DTI) is predictable from SNPs;

Holds up in independent, non-overlapping samples.

Brain measures are arguably* a good target for genetic analysis – may be easier to find genetic variants that directly affect the brain



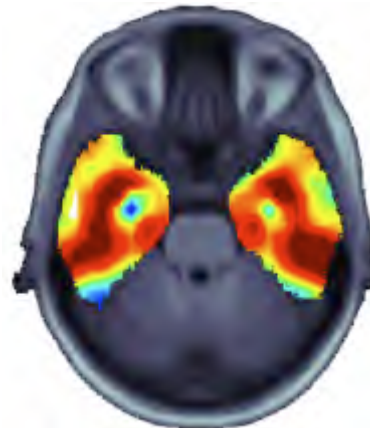
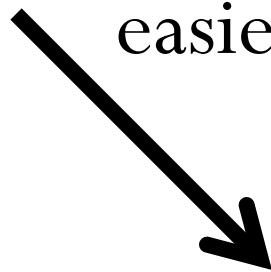
difficult



May require 10,000-30,000 people
e.g., the Psychiatric Genetics
Consortium studies



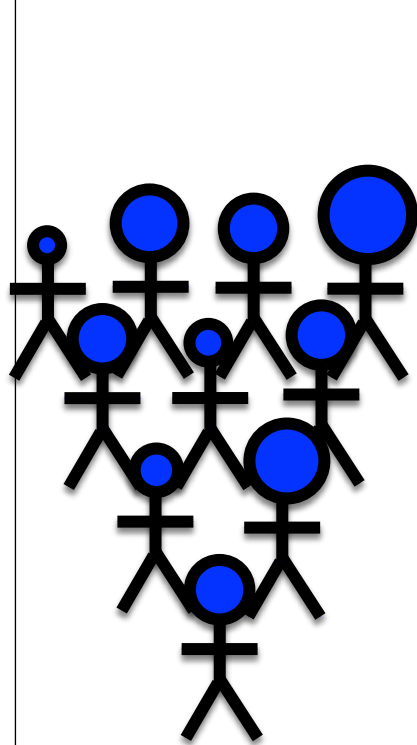
easier?



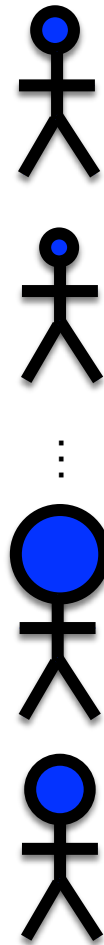
Gene variants may affect brain measures directly, many brain measures relate to disease status, they can be precisely and reproducibly measured



Finding Genetic Variants Influencing Brain Structure



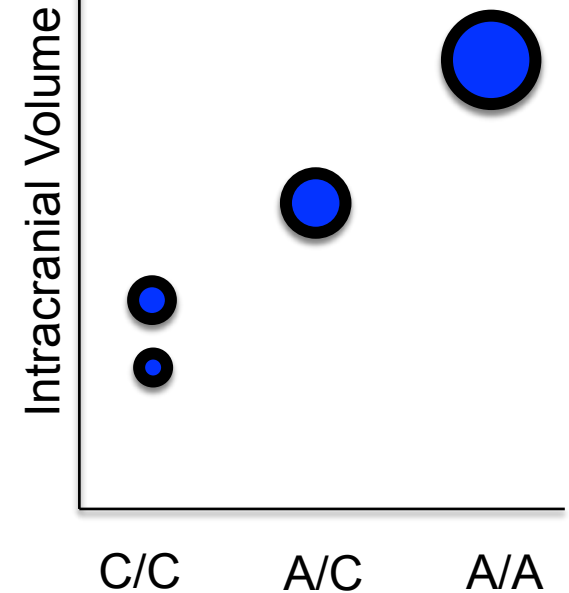
Phenotype



| | |
|-------|---------|
| CTAGT | CAGCGCT |
| CTAGT | CAGCGCT |
| CTAGT | CAGCGCT |
| CTAGT | CAGCGCT |
| ... | |
| CTAGT | AAGCGCT |
| CTAGT | AAGCGCT |
| CTAGT | AAGCGCT |
| CTAGT | CAGCGCT |

SNP

Genotype



Association

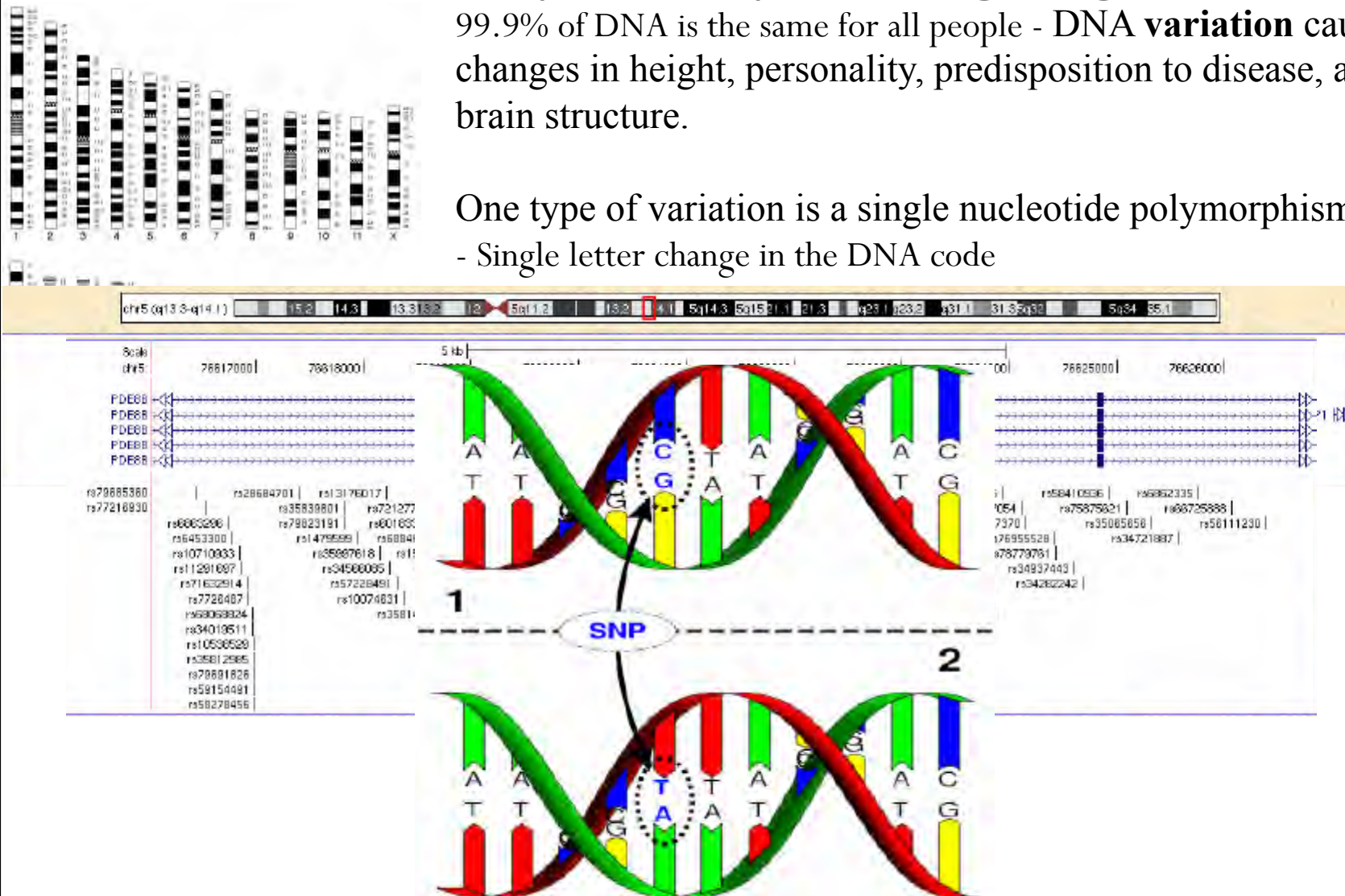
What do genome wide association studies (GWAS) try to find?

- common genetic *variants* related to a brain measure, or a disease, or a trait such as obesity, found by searching the genome

99.9% of DNA is the same for all people - DNA **variation** causes changes in height, personality, predisposition to disease, and brain structure.

One type of variation is a single nucleotide polymorphism (SNP)

- Single letter change in the DNA code



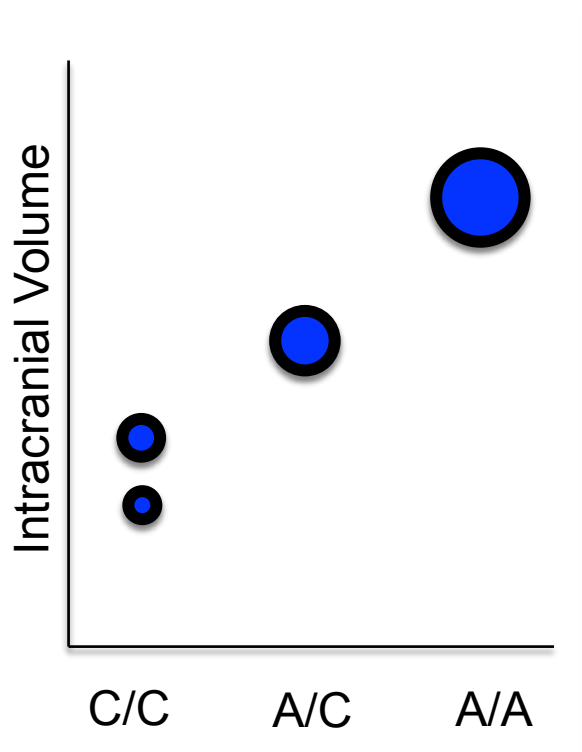
Single Nucleotide Polymorphism (SNP)

Genome-wide Association Study

One SNP

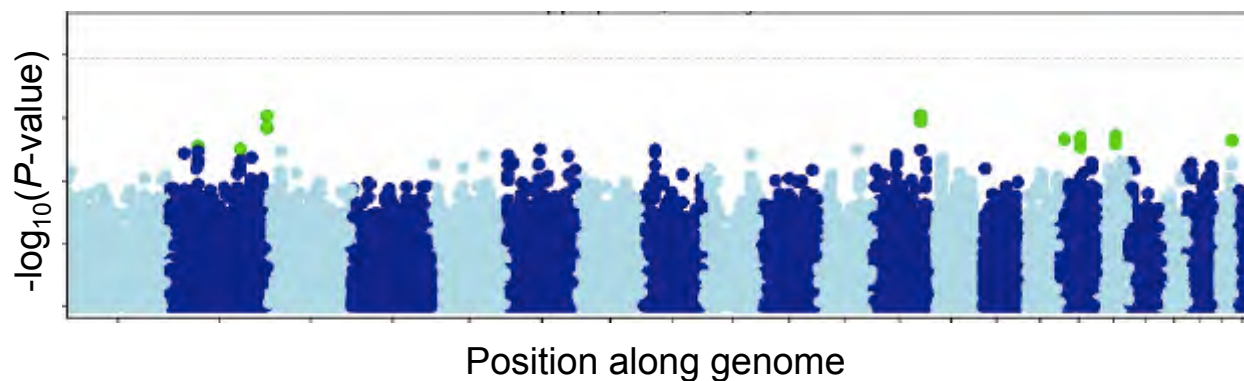
“Candidate gene” approach

e.g., *BDNF*



Screening

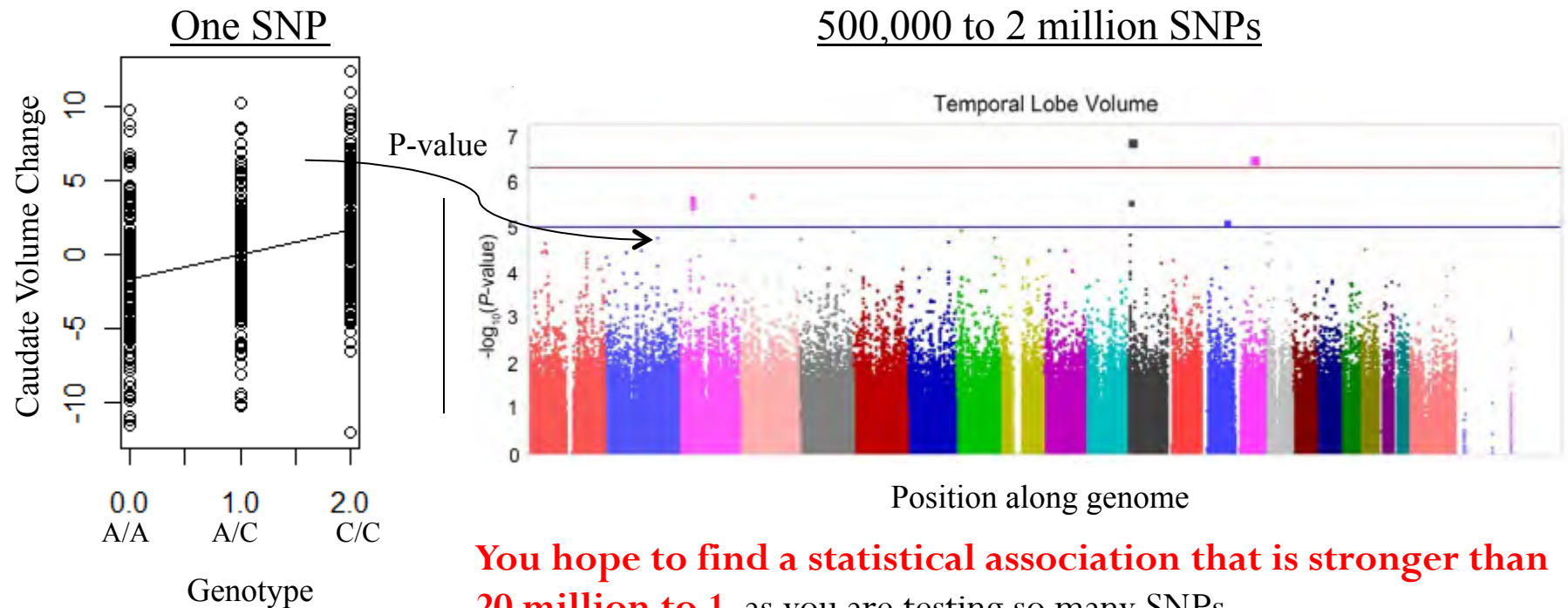
500,000 SNPs – 2,000,000 SNPs



An unbiased search to find where in the genome a variant is associated with a trait.

Genome-wide association study

Which genomic variants are associated with a trait?



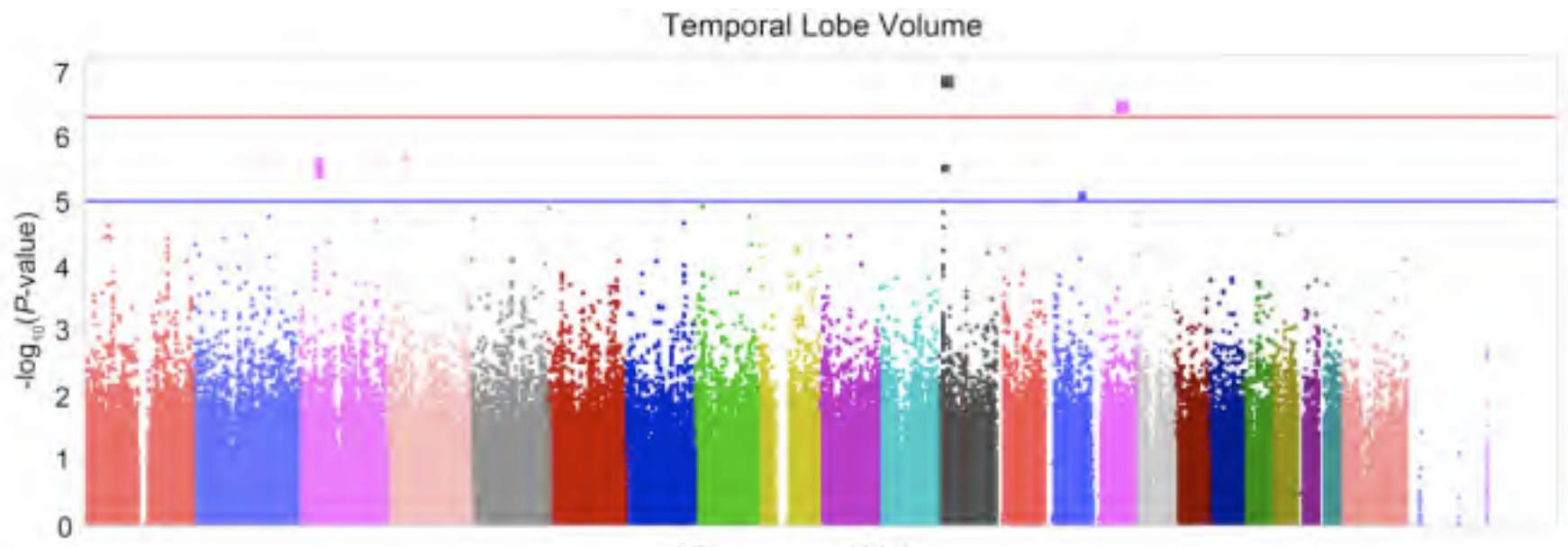
You hope to find a statistical association that is stronger than 20 million to 1, as you are testing so many SNPs

Usually need large samples (20,000 people)

GWAS = Finding common variants that explain some of the variation in a trait.

First Genome-Wide Screens of Brain Images (2009-2010)

GRIN2b genetic variant was **suggestively associated** with 2.8% temporal lobe volume deficit; this was later replicated in a non-overlapping cohort
The NMDA-type glutamate receptor is a target of memantine therapy;
first detected with GWAS in **N=742 subjects from the ADNI cohort**

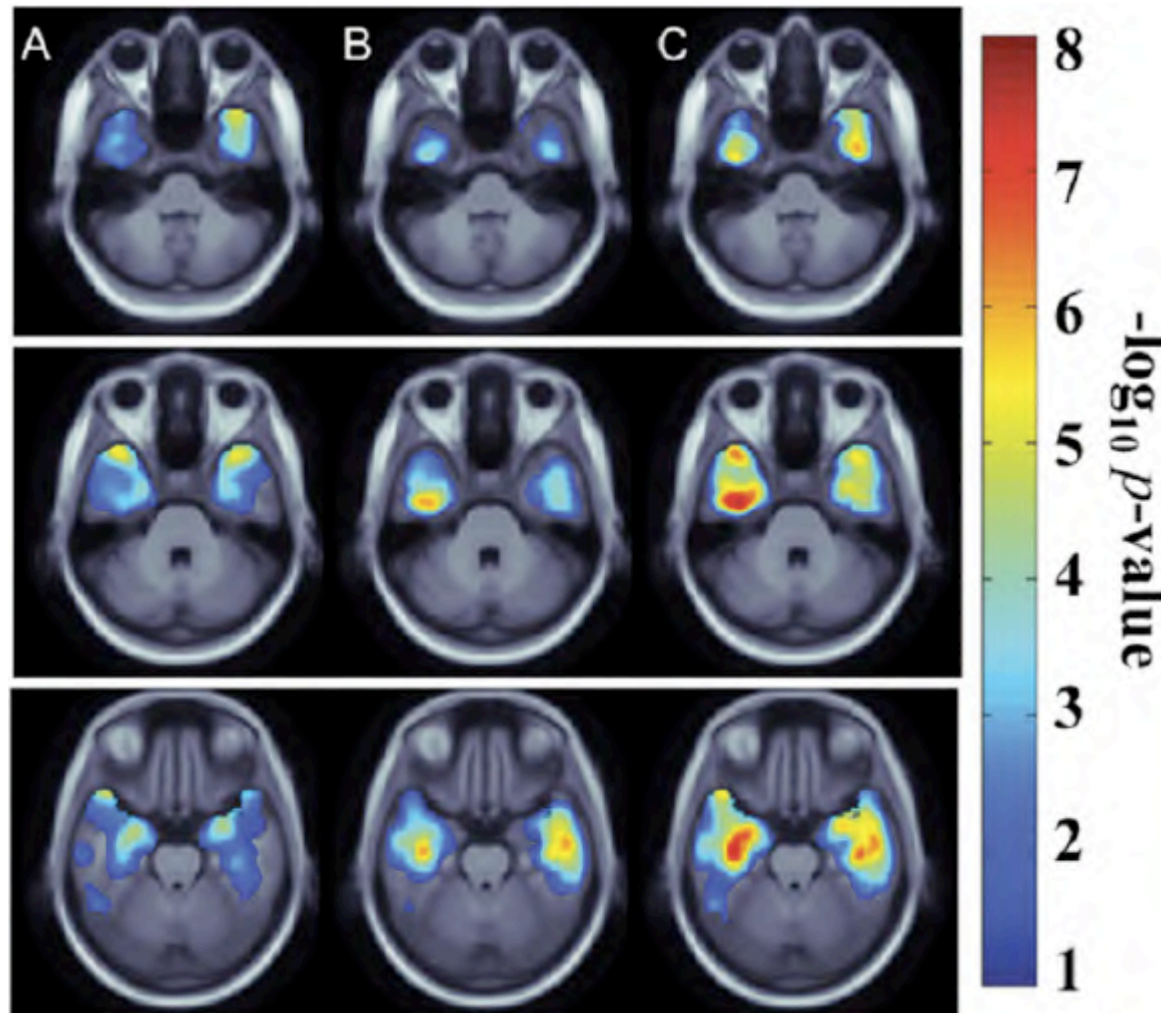


GRIN2b is over-represented in AD

- could be considered an Alzheimer's disease risk gene
- needs replication

Jason L. Stein¹, Xue Hua PhD¹, Jonathan H. Morra PhD¹, Suh Lee¹, April J. Ho¹, Alex D. Leow MD PhD^{1,2}, Arthur W. Toga PhD¹, Jae Hoon Sul³, Hyun Min Kang⁴, Eleazar Eskin PhD^{3,5}, Andrew J. Saykin PsyD⁶, Li Shen PhD⁶, Tatiana Foroud PhD⁷, Nathan Pankratz⁷, Matthew J. Huentelman PhD⁸, David W. Craig PhD⁸, Jill D. Gerber⁸, April Allen⁸, Jason J. Corneveaux⁸, Dietrich A. Stephan⁸, Jennifer Webster⁸, Bryan M. DeChairo PhD⁹, Steven G. Potkin MD¹⁰, Clifford R. Jack Jr MD¹¹, Michael W. Weiner MD^{12,13}, Paul M. Thompson PhD^{1,*}, and the ADNI (2010). **Genome-Wide Analysis Reveals Novel Genes Influencing Temporal Lobe Structure with Relevance to Neurodegeneration in Alzheimer's Disease**, *NeuroImage* 2010.

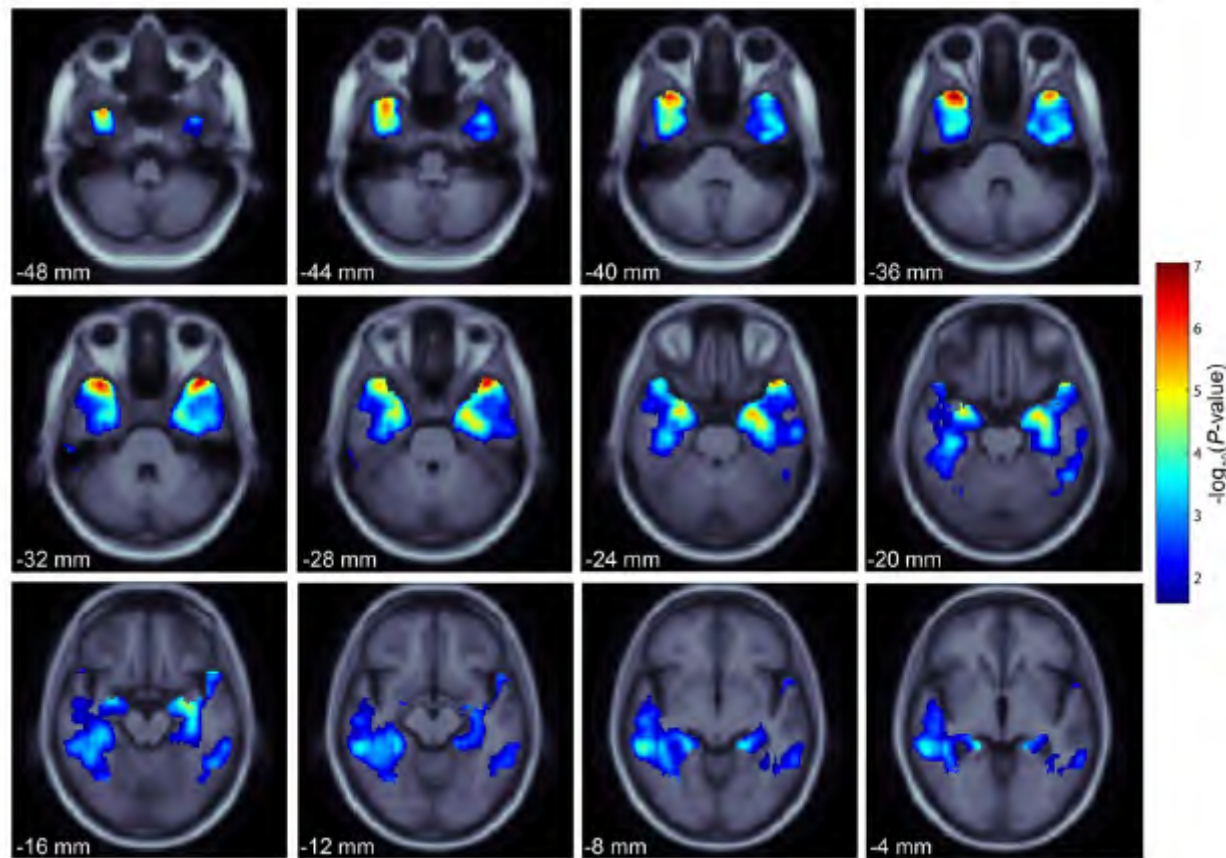
**GRIN2b (glutamate receptor) genetic variant associates with brain volume
in these regions; TT carriers have 2.8% more temporal lobe atrophy**



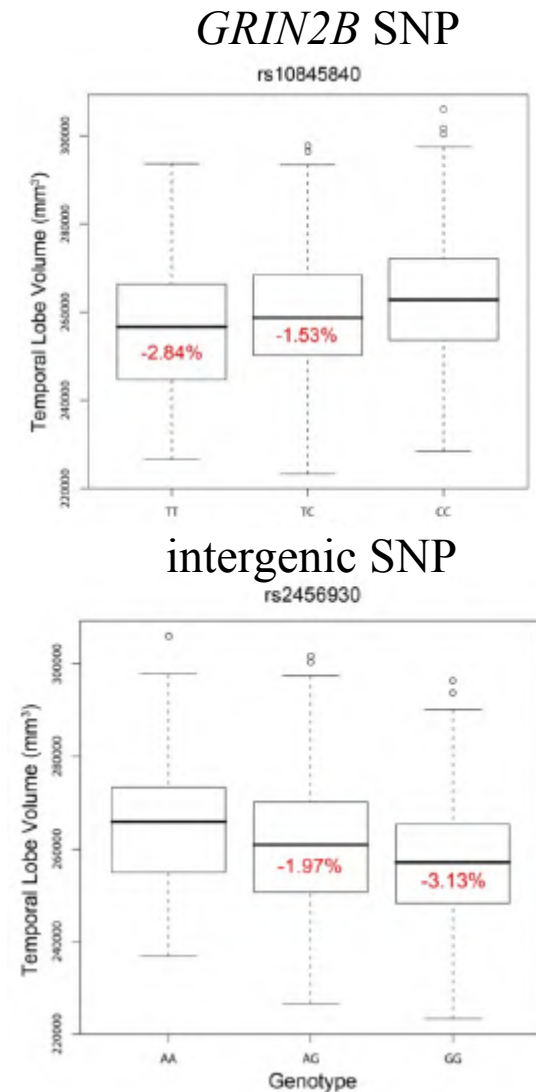
Effect was later
replicated in
a younger cohort
(Kohannim 2011)

Jason L. Stein¹, Xue Hua PhD¹, Jonathan H. Morra PhD¹, Suh Lee¹, April J. Ho¹, Alex D. Leow MD PhD^{1,2}, Arthur W. Toga PhD¹, Jae Hoon Sul³, Hyun Min Kang⁴, Eleazar Eskin PhD^{3,5}, Andrew J. Saykin PsyD⁶, Li Shen PhD⁶, Tatiana Foroud PhD⁷, Nathan Pankratz⁷, Matthew J. Huentelman PhD⁸, David W. Craig PhD⁸, Jill D. Gerber⁸, April Allen⁸, Jason J. Corneveaux⁸, Dietrich A. Stephan⁸, Jennifer Webster⁸, Bryan M. DeChairo PhD⁹, Steven G. Potkin MD¹⁰, Clifford R. Jack Jr MD¹¹, Michael W. Weiner MD^{12,13}, Paul M. Thompson PhD^{1,*}, and the ADNI (2010). **Genome-Wide Analysis Reveals Novel Genes Influencing Temporal Lobe Structure with Relevance to Neurodegeneration in Alzheimer's Disease, NeuroImage, 2010.**

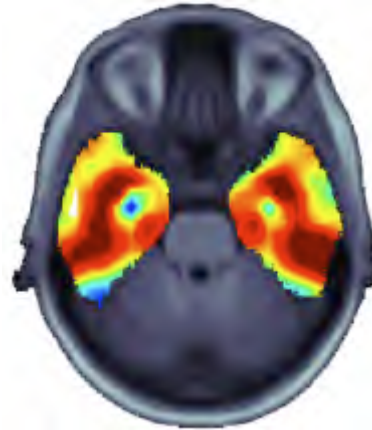
Effect of carrying adverse SNP is ~1.4%
lower volume per allele, same as ENIGMA's
top SNP



GRIN2B SNP (rs10845840)



Brain measures are a good target for genetic analysis – common DNA variation affects them and they relate to disease status



**STEP 2 – OUR STUDY FOUND
THIS CONNECTION**
 $P = 1.26 \times 10^{-7}$; later replicated

**STEP 1 – THIS
CONNECTION
WAS WELL-ESTABLISHED**

$P = 5.19 \times 10^{-11}$

Genetic Variation
GRIN2B
(rs10845840)

Imaging Biomarker
Related to Illness
Temporal Lobe Volume

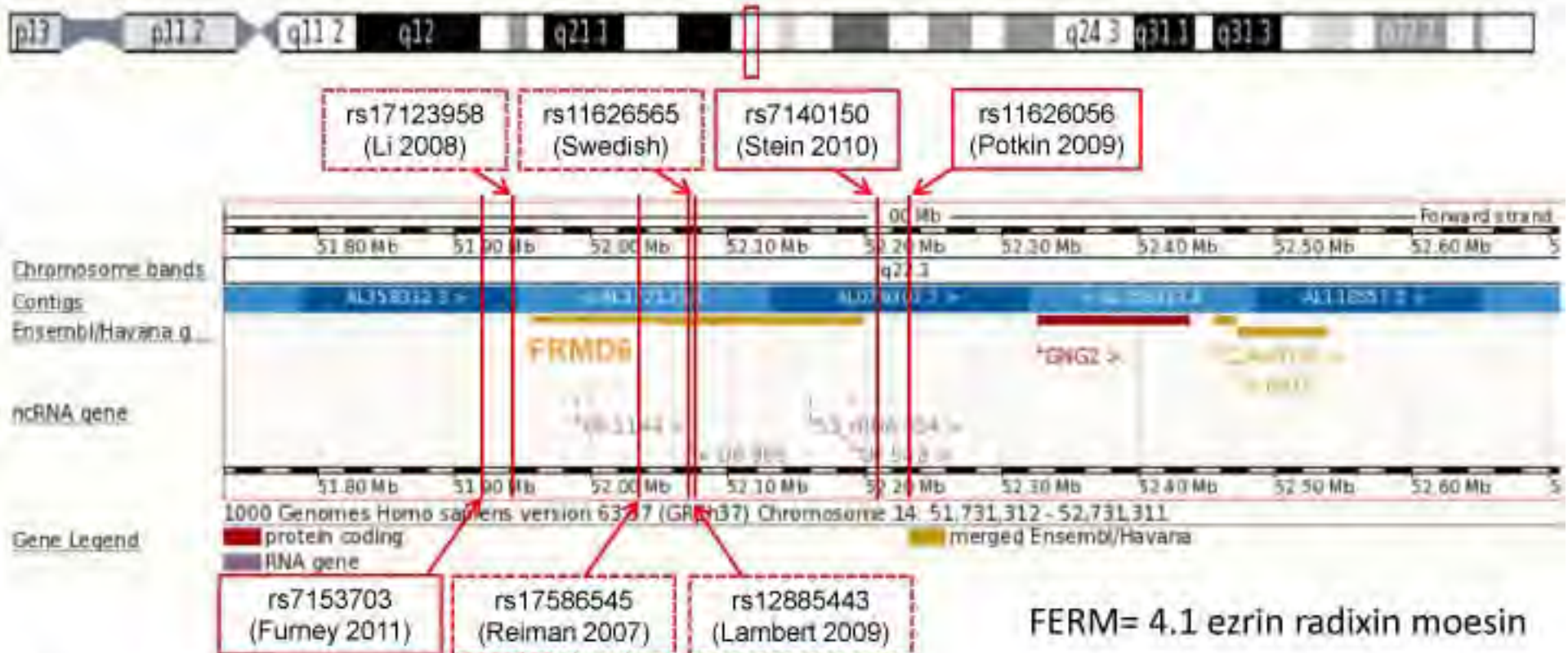
Diagnostic Status
Healthy elderly vs. AD or
MCI

**STEP 3 – CAN LATER CHECK IF IT IS
ASSOCIATED WITH DISEASE, $P = 0.039$;
NEEDS REPLICATION**

FRMD6: FERM domain-containing protein 6

Detected in 3 imaging genetics studies (2 ADNI; 1 ADNI/ANM) and validated by case/control GWAS

Chr 14q22.1



Hong et al, Genome-wide and gene-based association implicates FRMD6 in Alzheimer disease. Hum Mutat. 2011 Dec 20. [Epub].

Across the four combined GWAS samples, *FRMD6* showed the highest non-APOE signal: $p = 2.6 \times 10^{-14}$.

Saykin, 12/27/11

| Source | SNP | Position | MAF | p-value | OR (95%CI) |
|--------------|------------|----------|--------|-----------------------|--------------------------|
| Stein 2010 | rs7140150 | 51080549 | 0.4566 | 4.77×10^{-7} | <i>n/a - Imaging QTL</i> |
| Potkin 2009 | rs11626056 | 51303026 | 0.3295 | 1.18×10^{-8} | <i>n/a - Imaging QTL</i> |
| Furney 2011 | rs7153703 | 50989572 | 0.2130 | 3.38×10^{-6} | <i>n/a - Imaging QTL</i> |
| Swedish | rs11626565 | 51143880 | 0.0599 | 2.45×10^{-5} | 1.89; 1.34-2.13 |
| Reiman 2007 | rs17586545 | 51104768 | 0.0334 | 4.18×10^{-5} | 1.88; 1.36-2.54 |
| Li 2008 | rs17123958 | 51011874 | 0.1040 | 7.59×10^{-5} | 2.12; 1.38-3.24 |
| Lambert 2009 | rs12885443 | 51145403 | 0.1769 | 5.34×10^{-4} | 1.16; 1.07-1.25 |

***FRMD6* gene story - Imaging Genetics can **take the lead** in uncovering disease-relevant genes**

Novel candidate gene for AD

First recognized in several **imaging genetics analyses**

- **later replicated** in a **large case/control cohort**
- and by reanalysis of prior case/control GWAS data.

Furney et al phenotype was ventricular volume

Potkin et al was local hippocampal volume

Stein et al was a voxel-based map of regional brain volume differences.

Odds ratios for *FRMD6* SNPs from the 4 GWAS studies in Hong et al range from 1.16 to 2.12 - larger than most top AD genes (*Nature Genetics*, April 2011)

But still well below *APOE* (OR ~ 3).

FRMD6 appears promising as a replicated candidate gene.

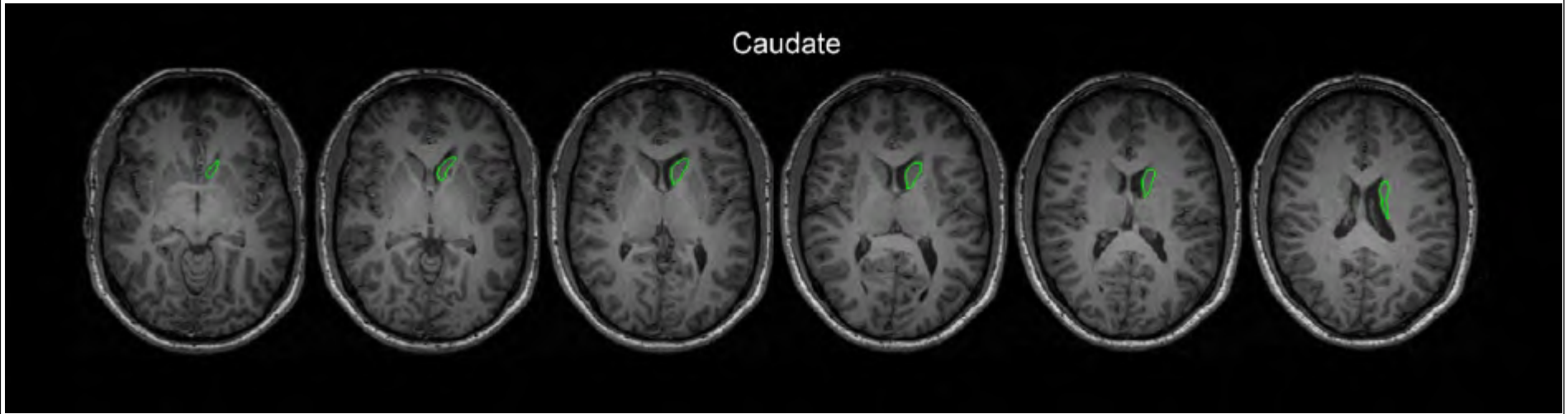
Little data so far on its biological function.

Beginnings of ENIGMA – 2 large populations; discover genes in one, then see if they replicate in the other

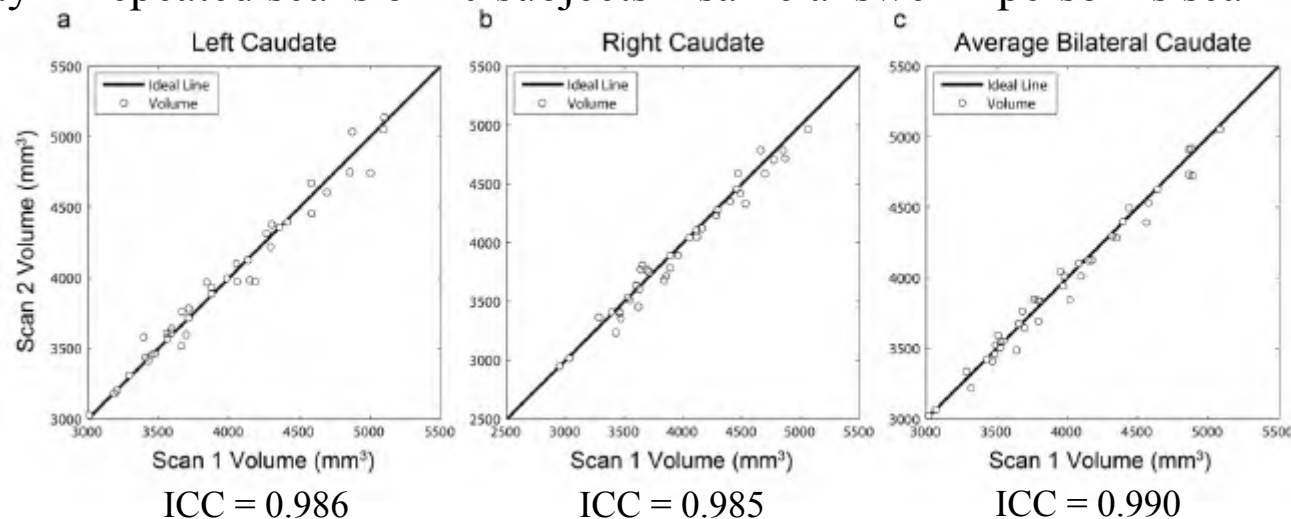


| Study Name | Subjects | Genetic Information | Age/Sex Distribution |
|--|--|---------------------|---|
| Alzheimer's Disease Neuroimaging Initiative (ADNI) | 734 healthy elderly, MCI, and AD | Illumina 610K GWAS | 75.5 ± 6.8 years 432 male/302 female |
| Brisbane Adolescent/Young Adult Longitudinal Twin Study (BLTS) | 464 young healthy MZ/DZ twins (239 families) | Illumina 610K GWAS | 23.7 ± 2.1 years 188 male/276 female |

Finding the Caudate Nucleus Automatically in 1198 MRI Scans – we can measure its volume reliably

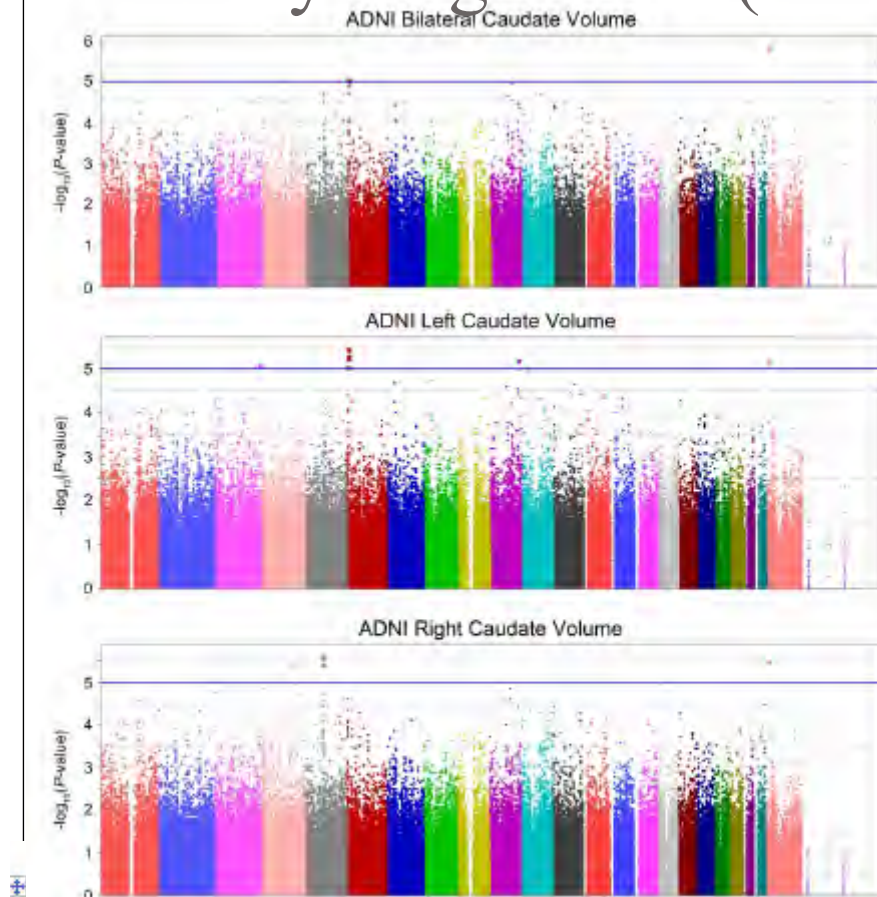


Reliability in repeated scans of 40 subjects – same answer if person is scanned again



Stein JL, Derrek P. Hibar¹, Sarah K. Madsen¹, Mathew Khamis¹, Katie L. McMahon², Greig I. de Zubicaray³, Narelle K. Hansell⁴, Grant W. Montgomery⁴, Nicholas G. Martin⁴, Margaret J. Wright⁴, Andrew J. Saykin⁵, Clifford R. Jack, Jr⁶, Michael W. Weiner^{7,8}, Arthur W. Toga¹, Paul M. Thompson¹, and the Alzheimer's Disease Neuroimaging Initiative* (2011). **Discovery and replication of dopamine-related gene effects on caudate volume in young and elderly populations (N=1198) using genome-wide search**, *Molecular Psychiatry*, 16: 927-937, September 2011.

Caudate association peak in *PDE8B* gene, replicates in 2nd young cohort (N=1198 people total)

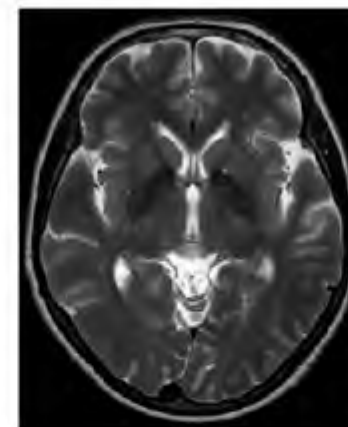


Same Gene implicated in Autosomal Dominant -Striatal Degeneration - Very severe effect on Caudate volume

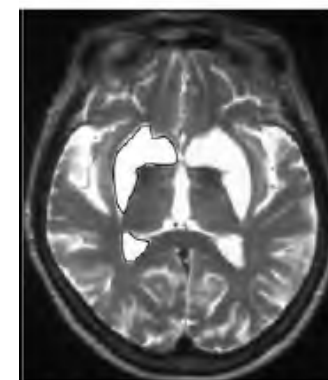
-In healthy people, affects Caudate volume

-Phosphodiesterase = key protein in the dopamine signaling cascade

-still not GW-significant in any one cohort alone



Control

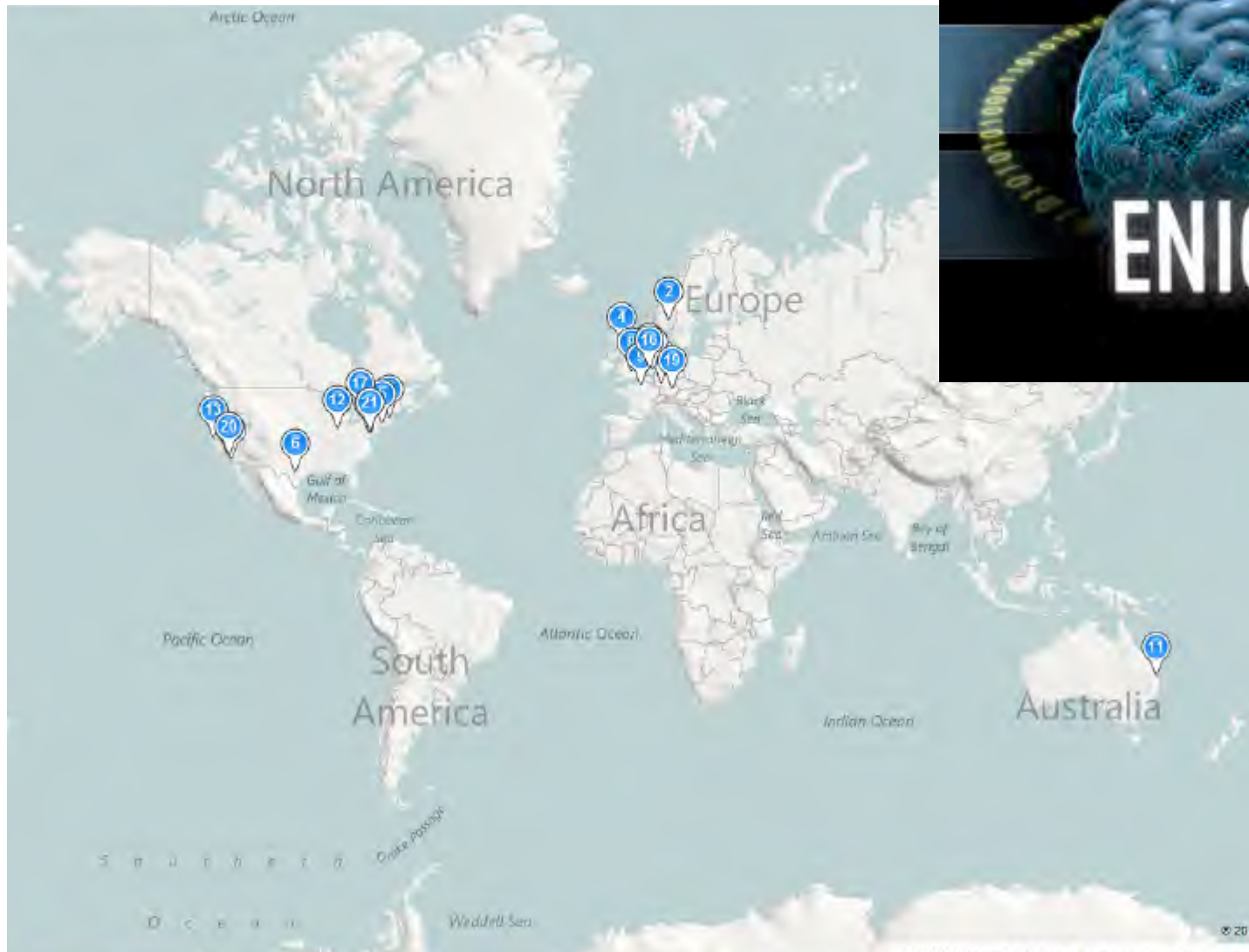


ADSD patient

| Chr | SNP | Position | Gene | ADNI | | | | | | BLTS | | | | | | |
|----------------------|-----------|-----------|-----------------|------|-------|-----|---------|------|-----------------------|-----------------------|----|-------|-----|---------|------|-------|
| | | | | A1 | Freq | N | β | SE | P | P <i>diag</i> | A1 | Freq | N | β | SE | P |
| <i>Right Caudate</i> | | | | | | | | | | | | | | | | |
| 5 | rs153030 | 76817227 | WDR41 | A | 0.499 | 731 | 147.4 | 31.0 | 2.36x10 ⁻⁶ | 6.00x10 ⁻⁶ | C | 0.524 | 462 | -83.2 | 33.2 | 0.012 |
| 5 | rs163035 | 76815798 | WDR41 | T | 0.499 | 734 | 147.2 | 31.0 | 2.47x10 ⁻⁶ | 6.00x10 ⁻⁶ | G | 0.524 | 461 | -83.2 | 33.2 | 0.013 |
| 5 | rs335636 | 76760355 | PDE8B, WDR41 | A | 0.500 | 733 | 143.8 | 30.9 | 3.90x10 ⁻⁶ | 8.00x10 ⁻⁶ | G | 0.525 | 464 | -81.1 | 33.0 | 0.014 |
| 4 | rs1299288 | 132606407 | | G | 0.230 | 734 | -169.4 | 36.6 | 4.43x10 ⁻⁶ | 5.00x10 ⁻⁶ | T | 0.770 | 464 | -42.0 | 39.3 | 0.286 |

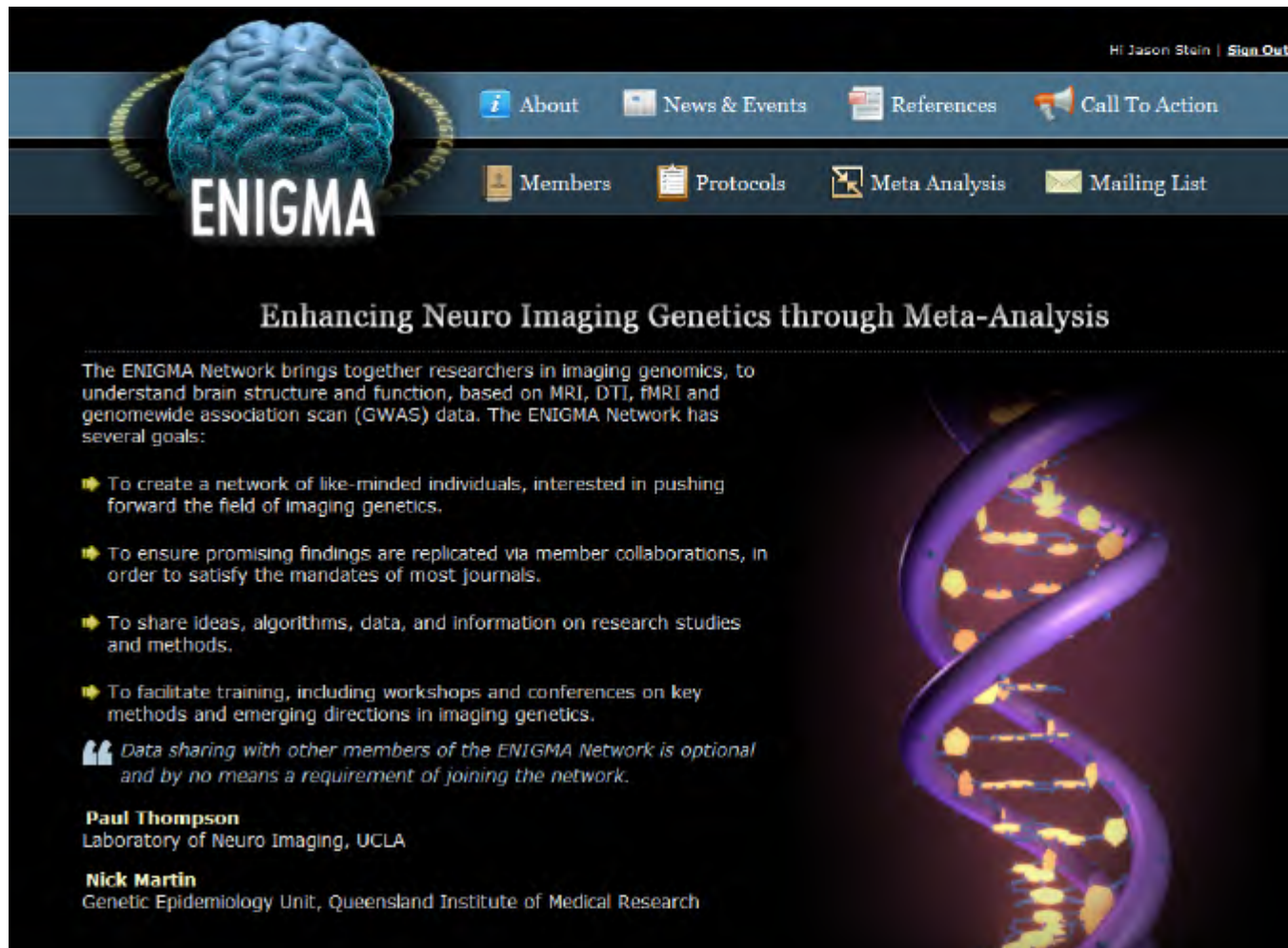
Initial Creation of the ENIGMA Consortium

Many sites were collecting MRI and DNA
– needed each other for replication



Replication through collaboration

<http://ENIGMA.loni.ucla.edu>

A screenshot of the ENIGMA website. The header features a blue brain with a yellow DNA helix around it, with the word "ENIGMA" in large white letters. To the right of the brain is a navigation bar with links: "About", "News & Events", "References", "Call To Action", "Members", "Protocols", "Meta Analysis", and "Mailing List". Below the navigation bar, the main heading reads "Enhancing Neuro Imaging Genetics through Meta-Analysis". The text below states: "The ENIGMA Network brings together researchers in imaging genomics, to understand brain structure and function, based on MRI, DTI, fMRI and genomewide association scan (GWAS) data. The ENIGMA Network has several goals:". A list of goals follows, each preceded by a yellow star icon. To the right of the text is a large, glowing purple and yellow DNA double helix. At the bottom, two names and affiliations are listed: "Paul Thompson, Laboratory of Neuro Imaging, UCLA" and "Nick Martin, Genetic Epidemiology Unit, Queensland Institute of Medical Research".

Hi Jason Stein | [Sign Out](#)


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[Members](#) [Protocols](#) [Meta Analysis](#) [Mailing List](#)

Enhancing Neuro Imaging Genetics through Meta-Analysis

The ENIGMA Network brings together researchers in imaging genomics, to understand brain structure and function, based on MRI, DTI, fMRI and genomewide association scan (GWAS) data. The ENIGMA Network has several goals:

- ✦ To create a network of like-minded individuals, interested in pushing forward the field of imaging genetics.
- ✦ To ensure promising findings are replicated via member collaborations, in order to satisfy the mandates of most journals.
- ✦ To share ideas, algorithms, data, and information on research studies and methods.
- ✦ To facilitate training, including workshops and conferences on key methods and emerging directions in imaging genetics.

 *Data sharing with other members of the ENIGMA Network is optional and by no means a requirement of joining the network.*

Paul Thompson
Laboratory of Neuro Imaging, UCLA

Nick Martin
Genetic Epidemiology Unit, Queensland Institute of Medical Research

- >200 scientists, 12 countries; must have DNA and MRI scans
- Many new members joining, several Working Groups

Meta-Analysis – each site uploads its genome-wide scans

- see if any of 500,000+ common genetic variants affect brain volume, brain integrity on DTI, brain amyloid measured with PET
- each site's “vote” depends on how many subjects they assessed

Submissions

| Group ID | Project Name | Contact Person | Meta-Analysis | File Status |
|----------|---|--------------------------------|---------------|-------------|
| 44 | GOBS | John Blangero | INFO | STATUS |
| 78 | Max Planck Institute of Psychiatry, Munich | Philipp Sämann | INFO | STATUS |
| 83 | MGH / Genomic SuperStructure | Randy Buckner / Jordan Smoller | INFO | STATUS |
| 88 | Imagen | Roberto Toro | INFO | STATUS |
| 94 | QTwin | Jason Stein/Sarah Medland | INFO | STATUS |
| 101 | Norwegian Cognitive Neurogenetics | Thomas Espeseth | INFO | STATUS |
| 105 | Roel Ophof f- UCLA/UMC Utrecht | Kristel van Eijk | INFO | STATUS |
| 108 | ADNI | Li Shen | INFO | STATUS |
| 113 | LBC1936 | Lorna Lopez | INFO | STATUS |
| 114 | BIG Study | Barbara Franke/Alejandro Arias | INFO | STATUS |
| 148 | NESDA | Saskia Woudstra | INFO | STATUS |
| 149 | MooDS | Andreas Meyer-Lindenberg | INFO | STATUS |
| 151 | fBIRN | Theo G.M. van Erp | INFO | STATUS |
| 161 | Thematic Organized Psychosis Research (TOP) | Ole Andreassen | INFO | STATUS |
| 164 | NIMH-IRP | Francis McMahon | INFO | STATUS |

Total Subject Tally

N w/ Patient

6,496

N w/o Patients

4,716

Genetic Imputation – allows ENIGMA members to compare and combine their data



Differences in genotyping chips used require **imputation to the same reference sample so each group is studying the same SNPs.**

Imputation is similar to resampling in imaging – put everything on the same grid

ENIGMA1 – HapMap reference panel

ENIGMA2 – “1000 Genomes” (1KG) reference panel;

Use imputation protocol on ENIGMA website

Sites had to measure regional brain volumes from MRI with validated, automated software programs (e.g., Freesurfer, FSL; some sites ran both; there was extensive QC, outliers left in if visually verified)

| Study Name | Hippocampus | | Brain Volume | | ICV | |
|------------|-------------|------|--------------|------|----------|------|
| | <i>r</i> | N | <i>r</i> | N | <i>r</i> | N |
| ADNI | 0.87 | 657 | 0.67 | 657 | 0.94 | 657 |
| BFS | 0.84 | 215 | 0.84 | 215 | 0.82 | 215 |
| BIG | 0.72 | 2180 | 0.97 | 927 | 0.72 | 927 |
| fBIRN | 0.70 | 78 | 0.75 | 78 | 0.87 | 78 |
| IMAGEN | 0.72 | 518 | 0.93 | 518 | 0.91 | 518 |
| MooDS | 0.72 | 137 | N/A | N/A | N/A | N/A |
| NCNG | 0.63 | 327 | 0.96 | 327 | 0.97 | 327 |
| QTIM | 0.71 | 386 | 0.93 | 386 | 0.73 | 386 |
| SHIP | 0.86 | 24 | 0.96 | 24 | 0.93 | 24 |
| SHIP-TREND | 0.68 | 24 | 0.98 | 24 | 0.91 | 24 |
| TOP | 0.71 | 419 | 0.97 | 419 | 0.94 | 419 |
| UMCU | 0.61 | 181 | N/A | N/A | N/A | N/A |
| EPIGEN | 0.78 | 203 | N/A | N/A | N/A | N/A |
| GOBS | 0.76 | 724 | 0.99 | 726 | 0.94 | 726 |
| NIMH-IRP | 0.53 | 20 | 0.91 | 20 | 0.94 | 20 |
| COMBINED | 0.75 | 6093 | 0.95 | 4321 | 0.90 | 4321 |



The **correlation between software programs** is comparable to human interrater variability (ICC=0.75-0.95); important in deciding **which structures to prioritize**

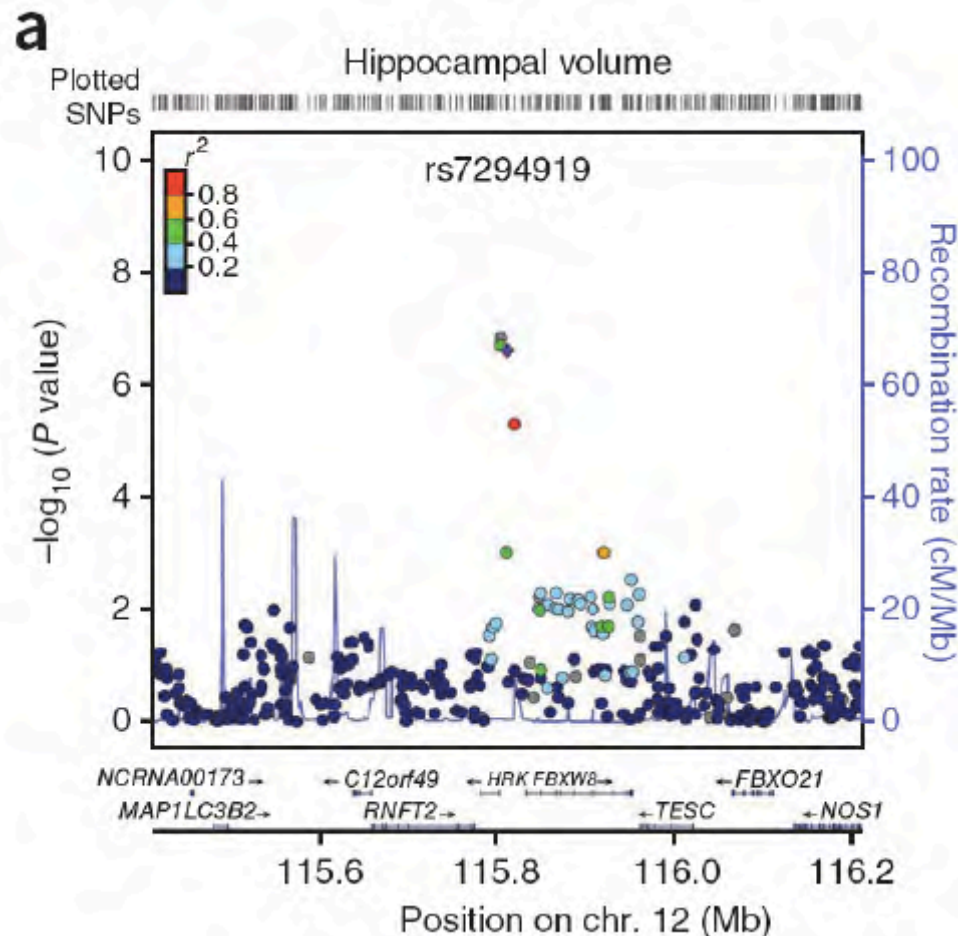
(Stein, Medland, Vasquez, Hibar, et al., *Nature Genetics*, 2012)

4 Nature Genetics papers (April 15 2012) - largest brain imaging studies in the world

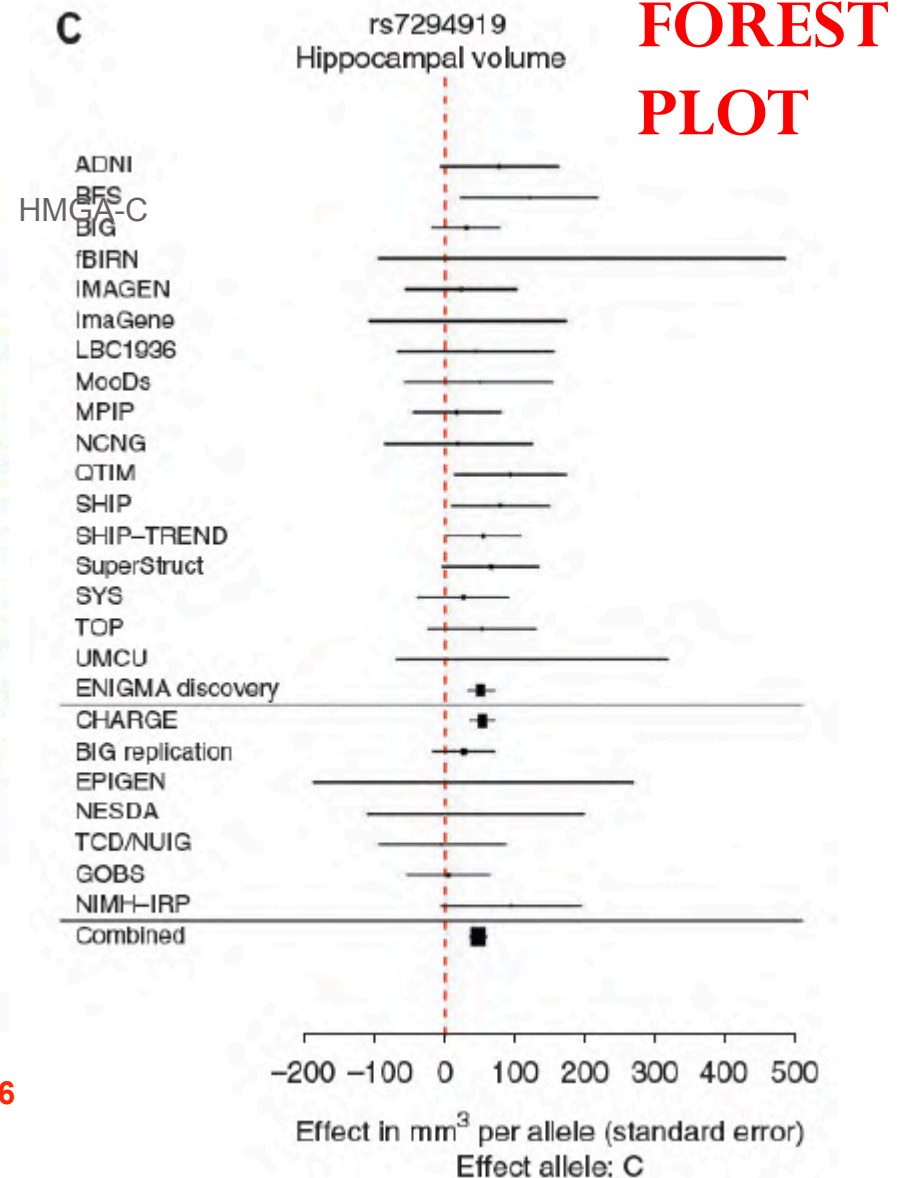
Chromosome 12 variant in *HMGA2* boosts brain volume by 9cc, IQ by 1.3 points

HP volume SNP ~ 3 years of aging,

Assoc. with 1.2% decrease in vol per allele

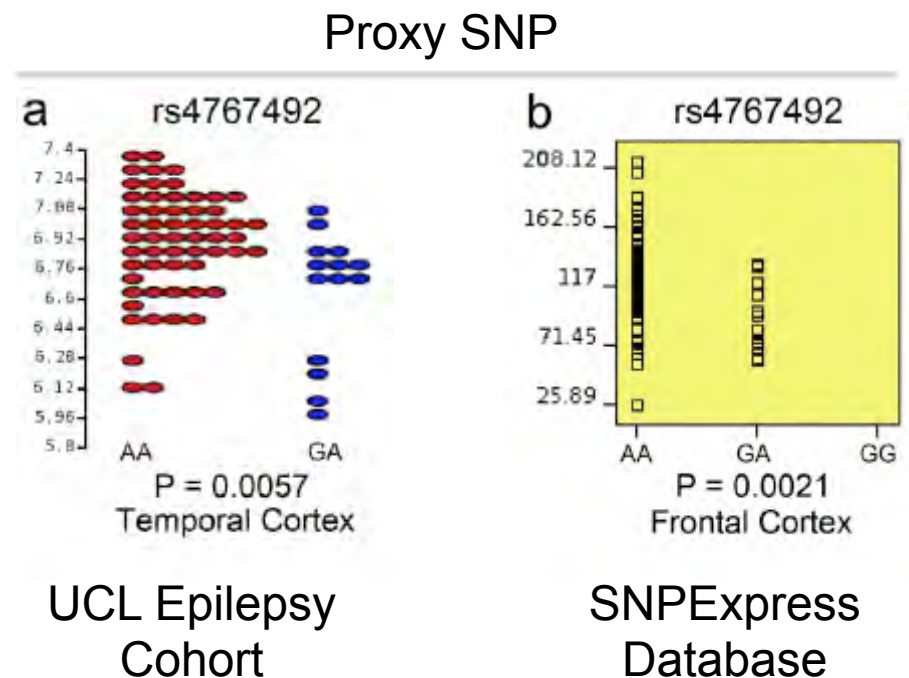
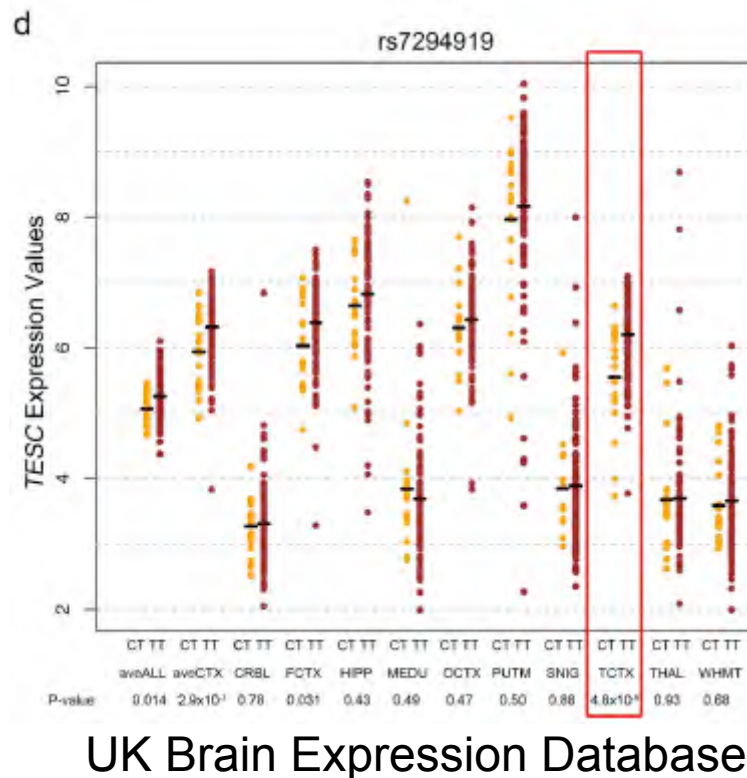


After Replication: **N = 21,151**; $P = 6.7 \times 10^{-16}$




(Stein, Medland, Vasquez, Hibar + **207 authors**, *Nature Genetics*, 2012)

The hippocampal volume SNP (or the closest available proxy) was associated with differences in the expression of a nearby gene, *TESC*, in brain tissue



(Stein, Medland, Vasquez, Hibar + **207 authors**, *Nature Genetics*, 2012)

Previously Studied Candidate Genes

| Gene | SNP (proxy) | P-value | Het. P-value |
|--|---|---|-----------------------|
| Full Discovery sample – including patients | | | |
| BDNF | rs6265 | 0.969 | 0.375 |
| TOMM40 | rs2075650 |  0.034 | 2.31x10 ⁻⁵ |
| CLU | rs11136000 | 0.287 | 0.186 |
| PICALM | rs3851179 | 0.079 | 0.035 |
| ZNF804A | rs1344706 | 0.325 | 0.908 |
| COMT | rs4680 | 0.211 | 0.827 |
| DISC1 | rs821616 (rs1754606 $r^2=1.00$) | 0.940 | 0.240 |
| NRG1 | rs35753505 (rs12681411 $r^2=0.835$) | 0.636 | 0.116 |
| DTNBP1 | rs1011313 | 0.416 | 0.832 |
| DTNBP1 | rs1018381 (rs875463 $r^2=1.00$) | 0.882 | 0.431 |

Previously studied candidate polymorphisms **showed little association** to hippocampal volume; Het. P-value – tests for heterogeneity of allele frequency across cohorts; some cohorts include AD patients

HMGA2 gene, Brain Size, and IQ

rs10784502

ICV

Intelligence

- Carriers of the C allele of rs10784502 in the *HMGA2* gene had **0.5% bigger intracranial volume** (9 cc, or 2 teaspoons)
- Also had **1.3 points higher full-scale IQ** per allele (N=1642; Beta(SE)=1.29(0.47); $P=0.0073$).
- This genetic variant **is associated with height**
- Has a known role in cancer cell proliferation

This result was quite widely reported (*New York Times*, *TIME Magazine*; 30 countries worldwide); needs to be replicated

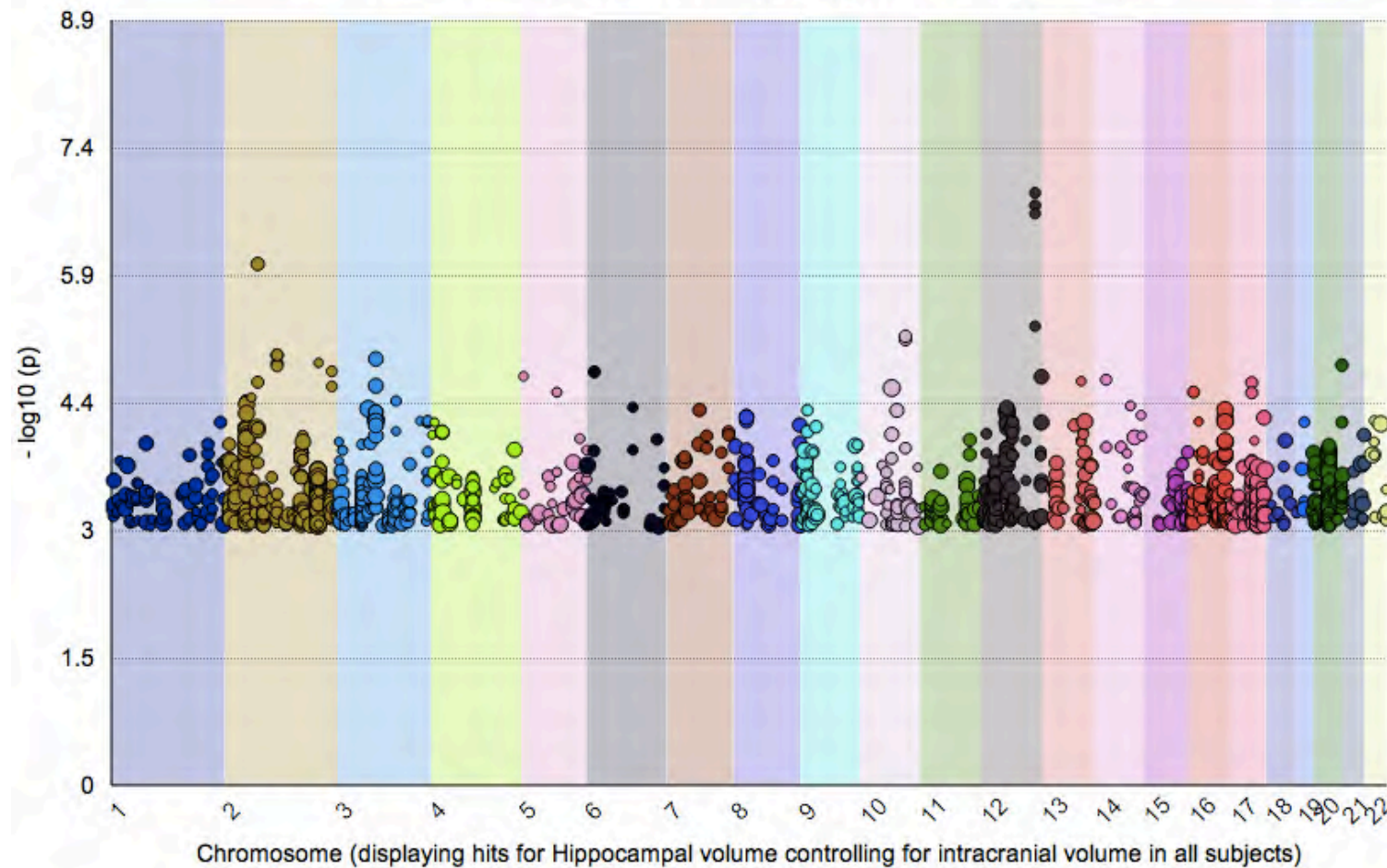
ENIGMA-Vis

You can look up any genes or SNPs you are interested in; see if they associate with brain measures; psychiatric GWAS and mouse QTL researchers have had success with it (try it)



Nic Novak

Manhattan plot showing all SNPs with $p < 0.001$



<http://enigma.ioni.ucla.edu/enigma-vis/>

(Novak et al., 2012)

ENIGMA Working Groups

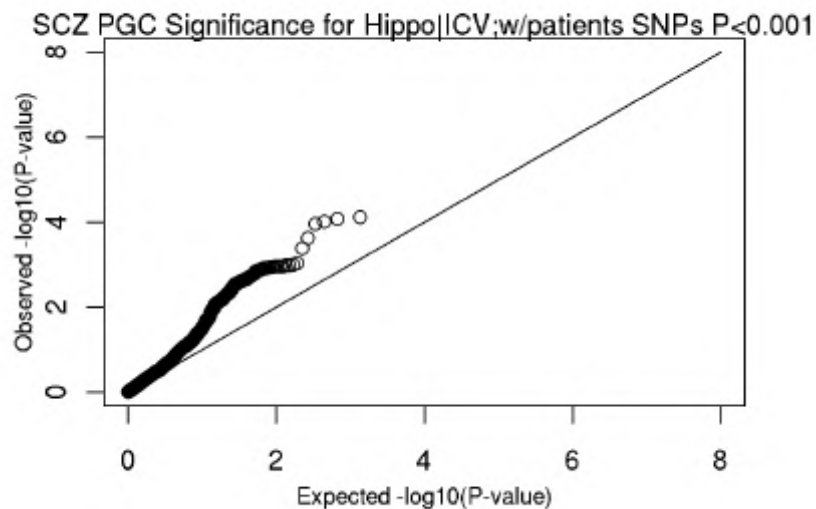
| <u>Project Name</u> | <u>Summary</u> | <u>Stage</u> |
|---------------------|--|---|
| ENIGMA2 | Subcortical Morphometry (caudate, amygdala, ...) | Image processing and new 1KG genetic imputation protocols now completed |
| ENIGMA-DTI | Diffusion Imaging Measures – integrity (FA, MD) of tracts, TBSS, anatomical connectivity, NxN connectomes | Phenotype harmonization; N=4000+; many cohorts joining; Protocol being beta-tested at 6 sites (Kochunov et al., OHBM 2012) |
| ENIGMA-PIB | Amyloid PET based measures | Just began – 4 large cohorts with PIB (AIBL in Australia, U. Pittsburgh, ADNI, [Wash U]) and several smaller ones |
| ENIGMA-PGC | How do psychiatric risk genes affect the brain? Do “brain genes” affect risk for SCZ, MDD, BPD, AUT, ADHD, ... | 4-pronged approach: reciprocal look-up; statistical conjunction; enrichment; polygenic testing |

ENIGMA + PGC Schizophrenia

Start with simple univariate look-ups, then move on to polygenic tests, ENIGMA2 structures

Enrichment Test - QQ Plot

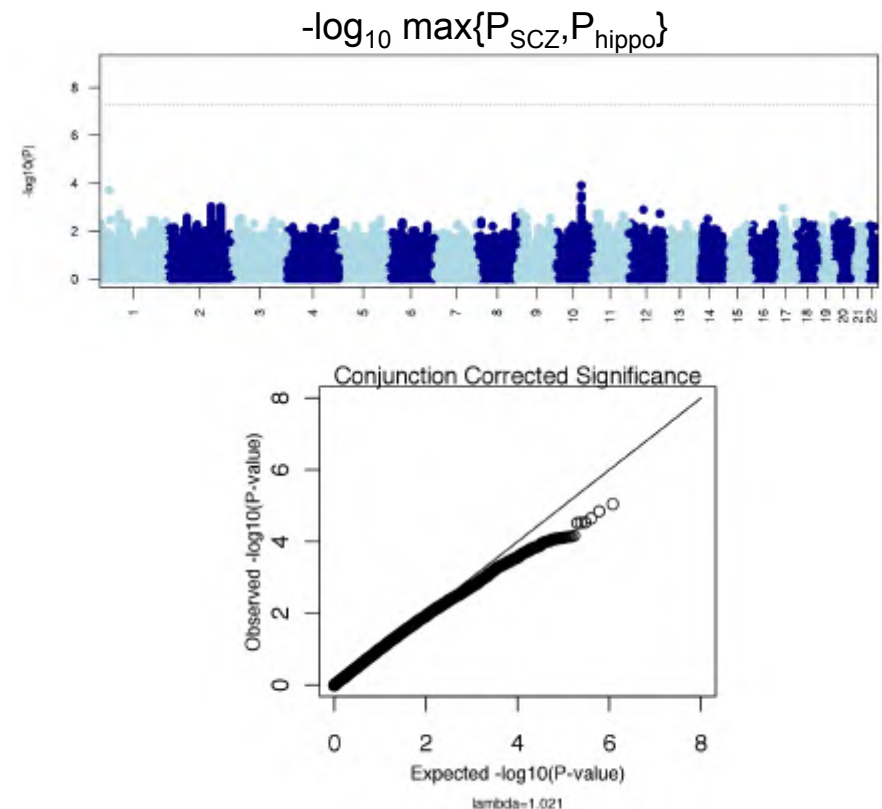
Do ENIGMA SNPs that may affect hippocampal volume (at $p < 0.001$) affect schizophrenia risk?



- The lambda value based on LD pruned SNPs is 1.401.
- The P -value for this lambda based on random draws from the LD-pruned distribution is 0.1081.
- No strong global effect of hippocampal SNPs on schizophrenia risk

Conjunction Analysis – very stringent test

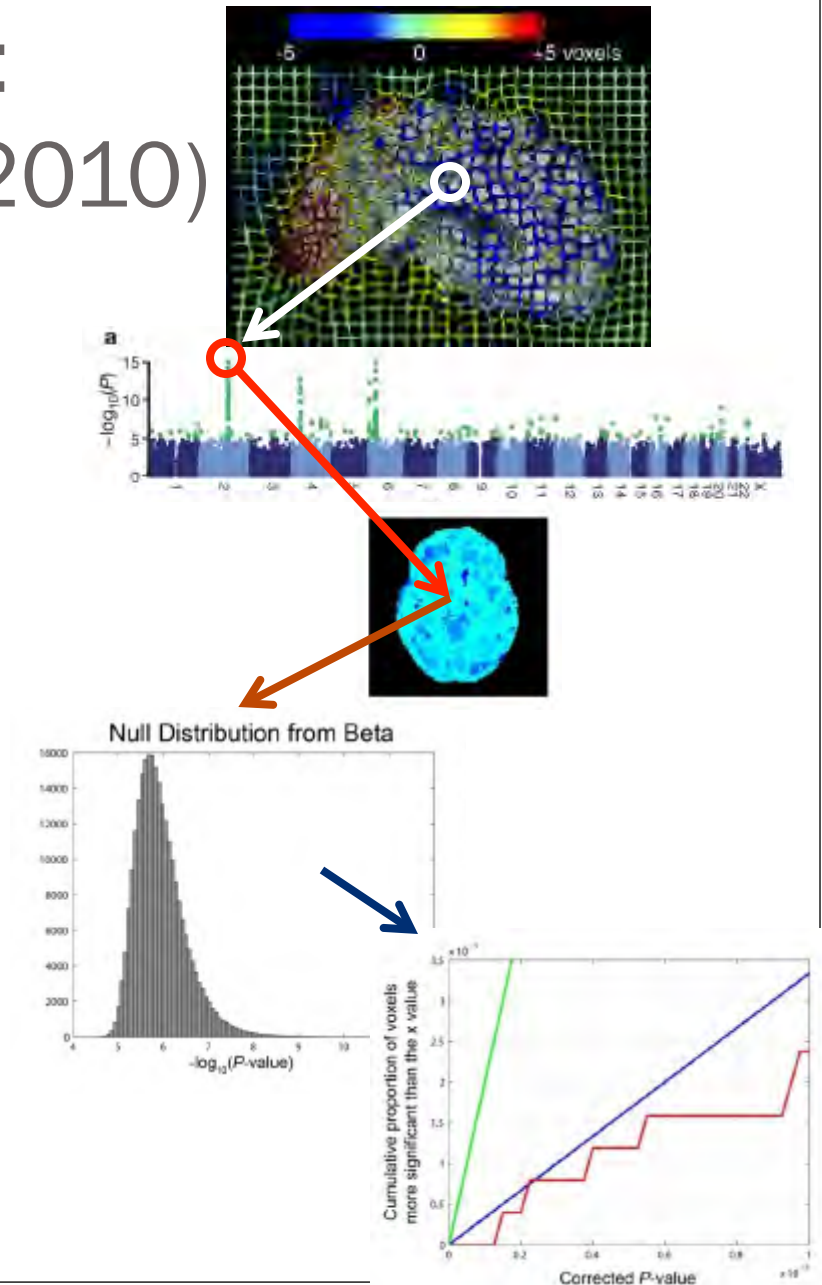
Is there evidence that any SNP is associated with a change in hippocampal volume **and** risk for schizophrenia?



With corrected significance, no strong joint associations observed.

You can search the **entire brain** and the genome at the same time:
“Voxelwise” GWAS (Stein 2010)

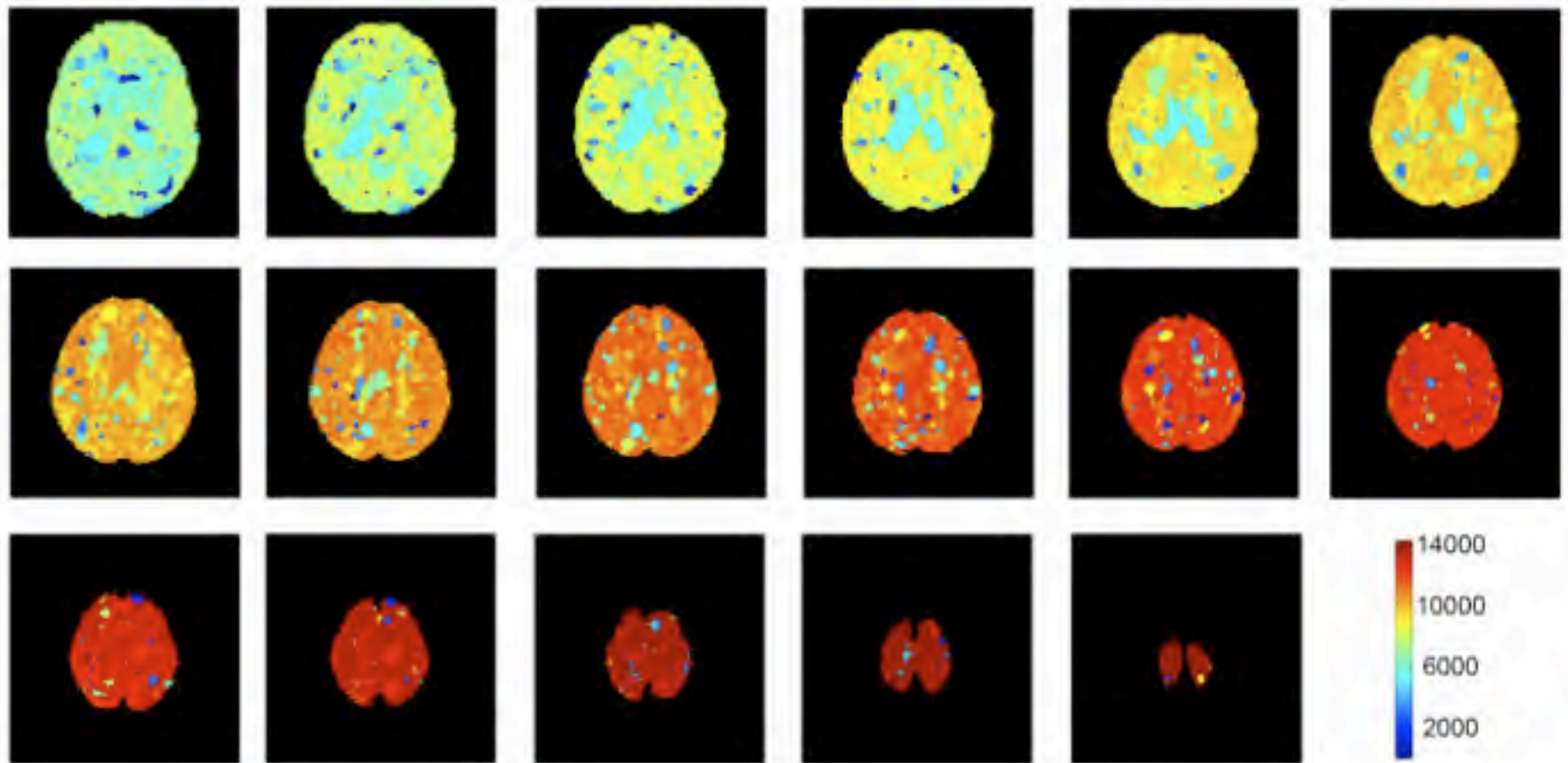
1. Volume difference at each voxel relative to a template serves as phenotype
2. Scan the genome for associations at each brain location (each voxel)
3. Select only the most associated SNP at each voxel
4. Adjust P -values through an inverse beta transformation (max of N null uniform distributions)
5. Correct for multiple comparisons across voxels using FDR



Voxelwise Genome-Wide Association Study (vGWAS; 719 subjects)

545,871 **SNPs** x 252,408 **voxels** = **138 billion tests** [10 days to run]

Discovers Most Associated SNP at each Voxel



Discovered XKR4, PIP4K2A, CSMD2, CADPS2, and PIP3-E genes relevant to brain and cytoskeletal structure; some previously associated with psychiatric disease.

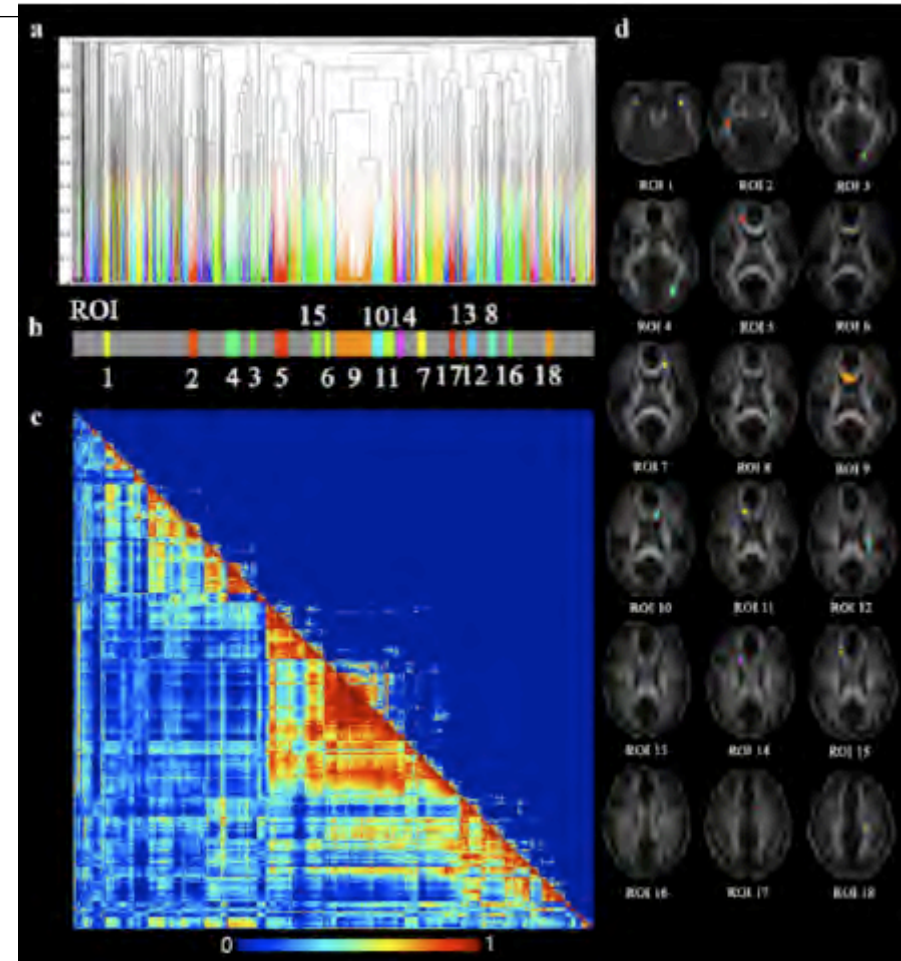
Jason L. Stein¹, Xue Hua PhD¹, Suh Lee¹, April J. Ho¹, Alex D. Leow MD PhD^{1,2}, Arthur W. Toga PhD¹, Andrew J. Saykin PsyD³, Li Shen PhD³, Tatiana Foroud PhD⁴, Nathan Pankratz⁴, Matthew J. Huentelman PhD⁵, David W. Craig PhD⁵, Jill D. Gerber⁵, April N. Allen⁵, Jason J. Corneveaux⁵, Bryan M. DeChairo PhD⁶, Steven G. Potkin MD⁷, Clifford R. Jack Jr MD⁸, Michael W. Weiner MD^{9,10}, Paul M. Thompson PhD^{1,*}, and the ADNI (2009). **Voxelwise Genome-Wide Association Study (vGWAS)**, *NeuroImage* 2010.

.....but Image-wide GWAS
only tests one voxel at a time,
as if they were totally
independent

Overlooks coherent patterns
of gene action
in the image

Want to Cluster Voxels
with Common Genetic Influences

Boosts the Power of GWAS in Images
(Chiang et al., J Neuroscience 2012)



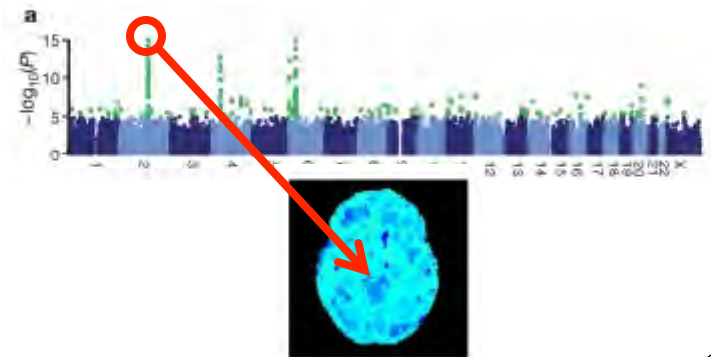
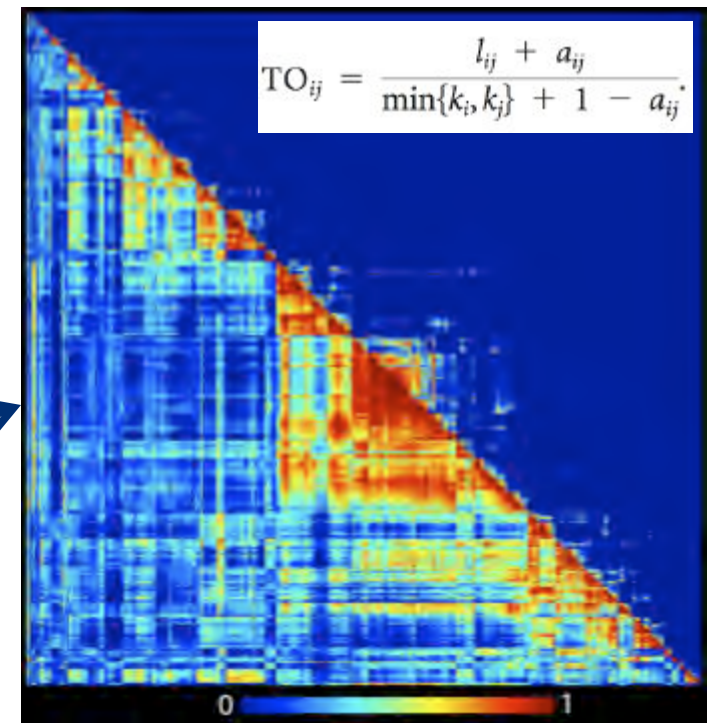
Gene Network Effects on Brain Microstructure and Intellectual Performance Identified in 472 Twins

Ming-Chang Chiang,^{1,2} Marina Barysheva,² Katie L. McMahon,³ Greig I. de Zubicaray,⁴ Kori Johnson,³ Grant W. Montgomery,⁵ Nicholas G. Martin,⁵ Arthur W. Toga,² Margaret J. Wright,⁵ Paul Shapshak,⁶ and Paul M. Thompson²

Cluster voxels based on their genetic correlation

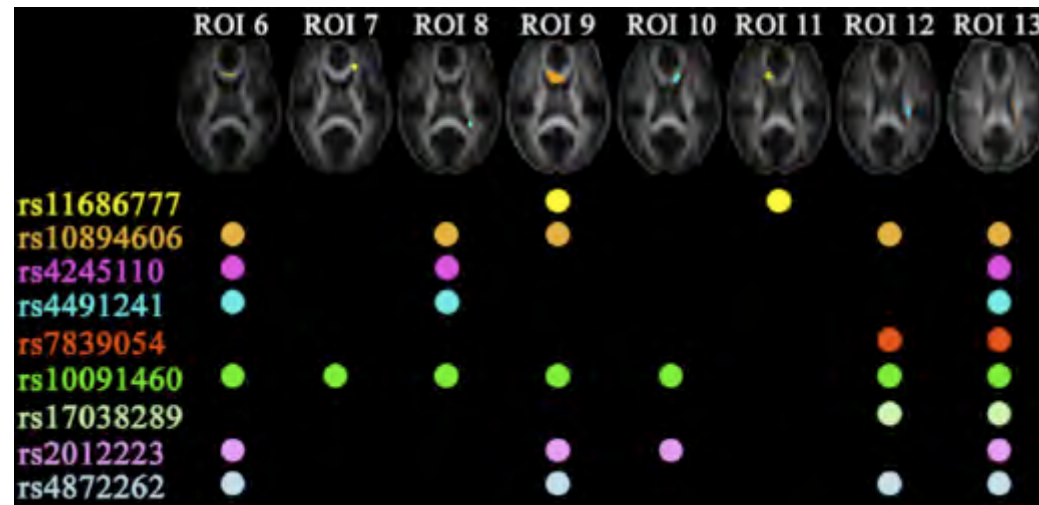
1. In twin or family designs, we can estimate the **genetic correlation between any two traits**, e.g. brain size and IQ, i.e., there may be a correlation between the genetic factors affecting the 2 traits
2. Apply same logic to **pairs of voxels in an image** – is there any genetic correlation? (cross-twin, cross-trait method)
3. $R_g(x,y)$ gives very dense network; thin it down by transforming to Topological Overlap index network, $TO(x,y)$ (Zhang & Horvath, 2005; better clusters)
4. Do hierarchical clustering of voxels with common genetic determination
5. Treat largest clusters as regions of interest
6. Run GWAS on these new ROIs
7. Much faster; does it also boost power?

4876x4876 matrix



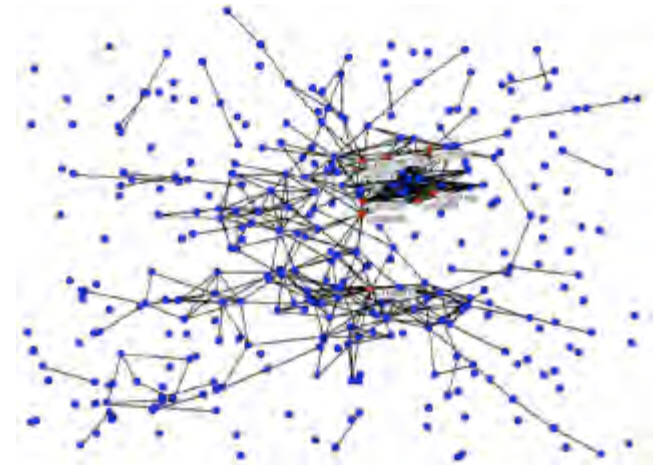
Genetic clustering boosts GWAS power

1. Many top hits now reach genome-wide significance ($N=472$) and replicate
2. Several SNPs affect multiple ROIs



3. Can form a network of SNPs that affect similar ROIs
4. It has a small-world, scale-free topology

(for more, see Chiang et al., J. Neurosci., 2012)



Genetic correlation between a blood biomarker and an image

1. Suppose you have a gene that affects a known blood or CSF biomarker, and you want to see if it also affects the brain, and if so, where

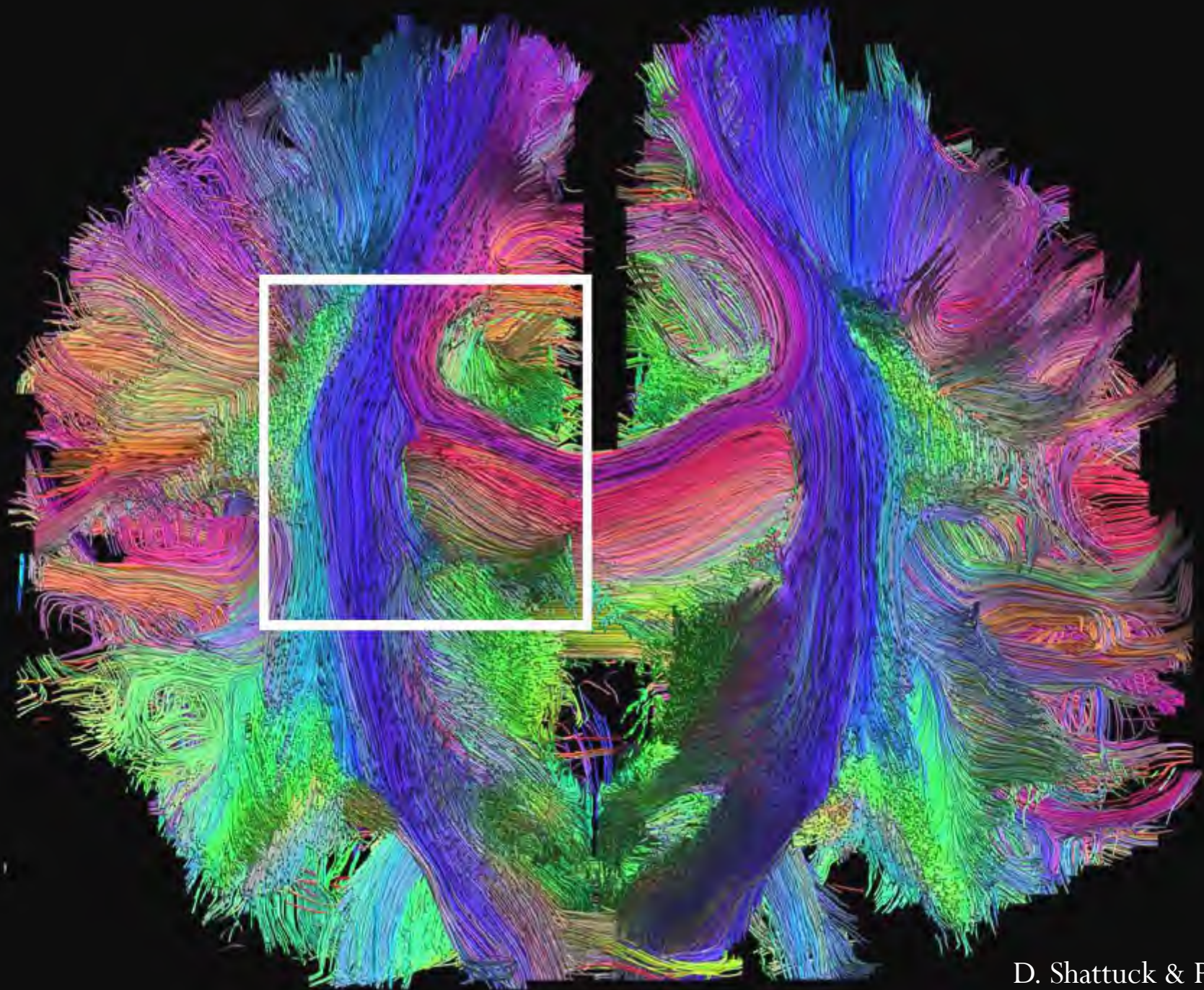
HFE gene -> transferrin levels in blood (buffers iron, vital for myelination)

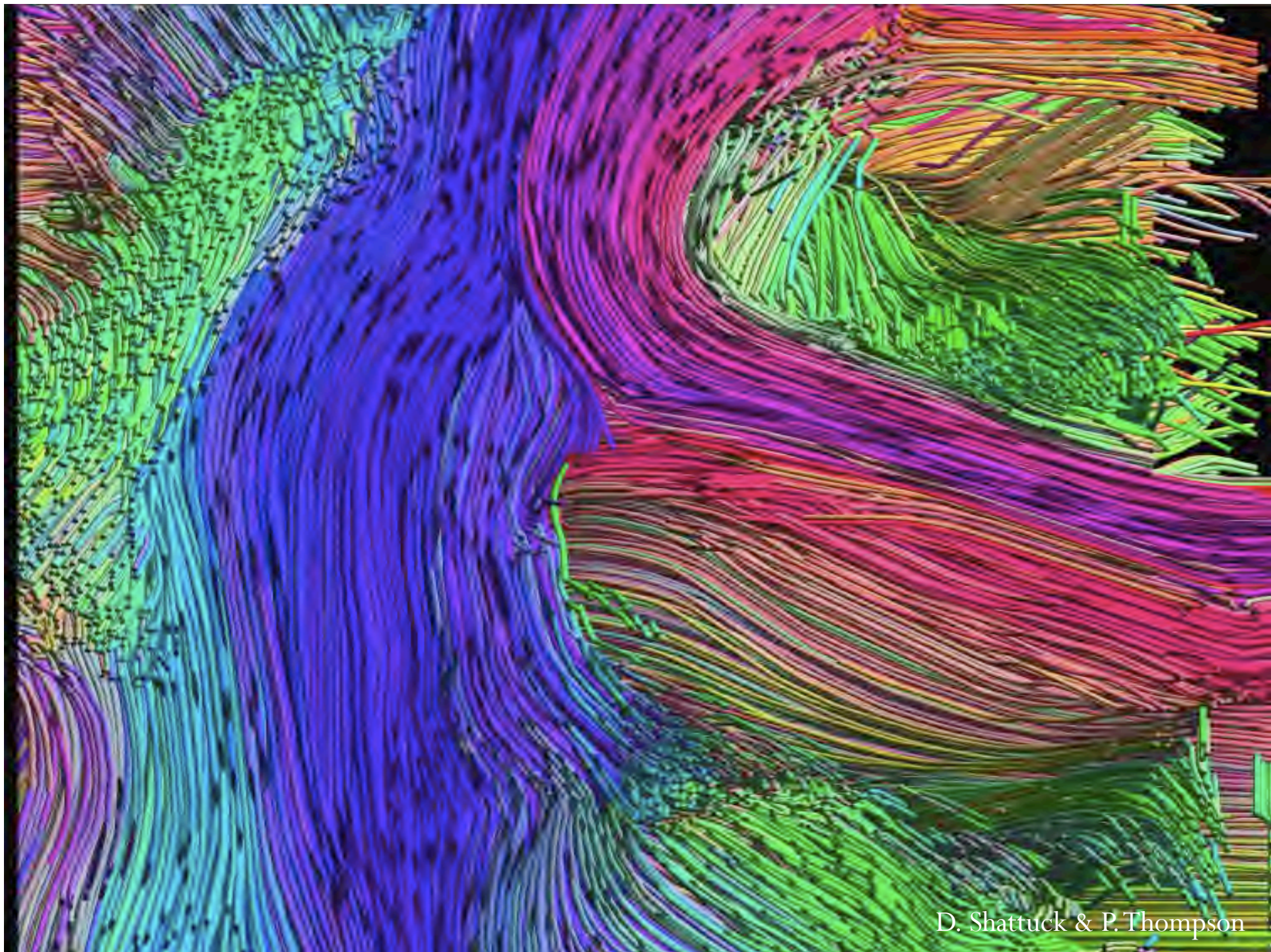
MTHFR gene -> homocysteine levels in blood (causes atrophy)

2. Find the parts of the brain that show genetic correlations with the blood measure (voxel-based cross-twin cross-trait association)
3. Test the SNP's association in just those regions of the brain, to boost power (for more, see Jahanshad et al., *PNAS*, 2011; Rajagopalan et al., submitted)

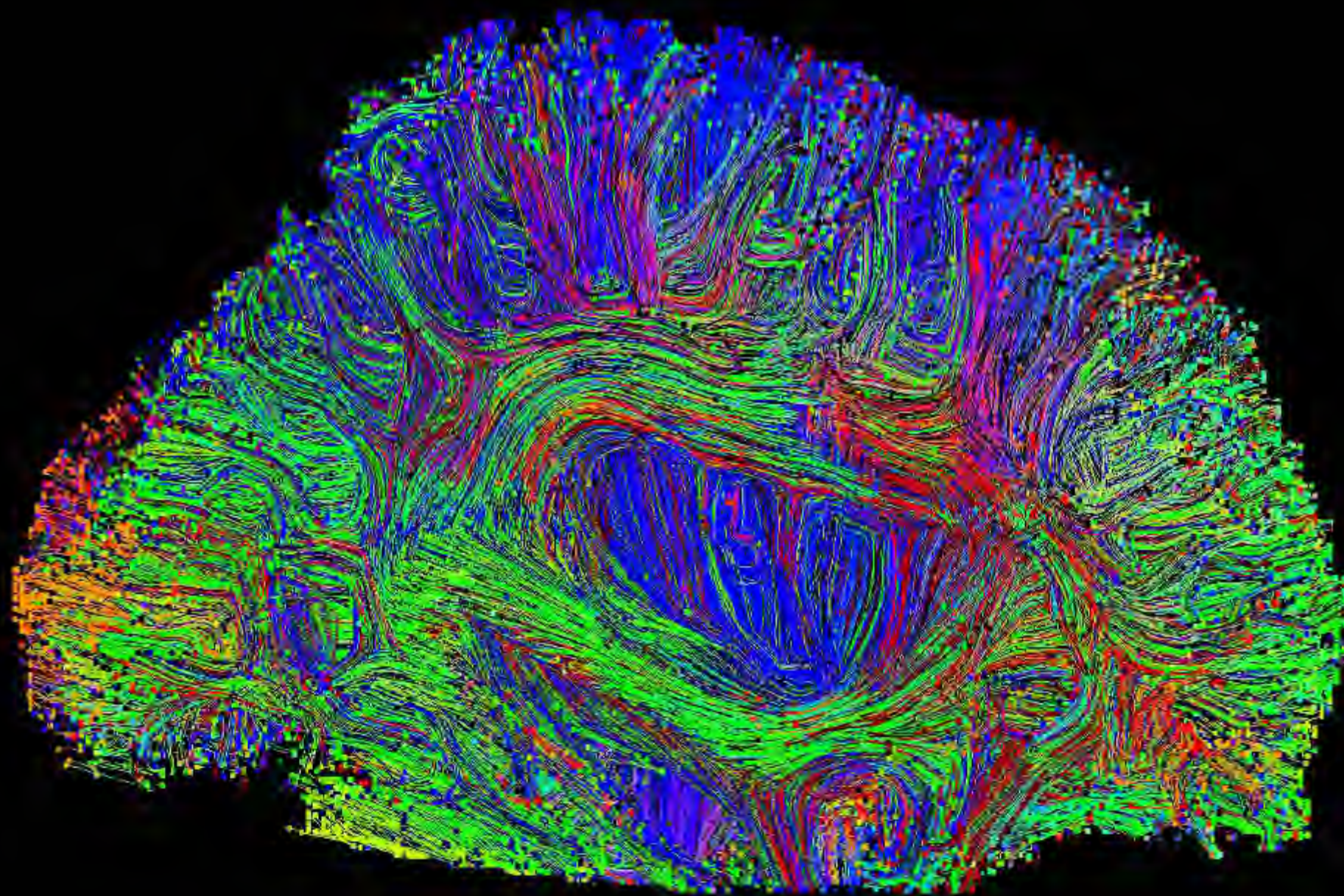
Brain structure in healthy adults is related to serum transferrin and the H63D polymorphism in the *HFE* gene

Neda Jahanshad^{a,b}, Omid Kohannim^a, Derrek P. Hibar^a, Jason L. Stein^a, Katie L. McMahon^c, Greig I. de Zubicaray^d, Sarah E. Medland^e, Grant W. Montgomery^e, John B. Whitfield^e, Nicholas G. Martin^e, Margaret J. Wright^e, Arthur W. Toga^a, and Paul M. Thompson^{a,1}

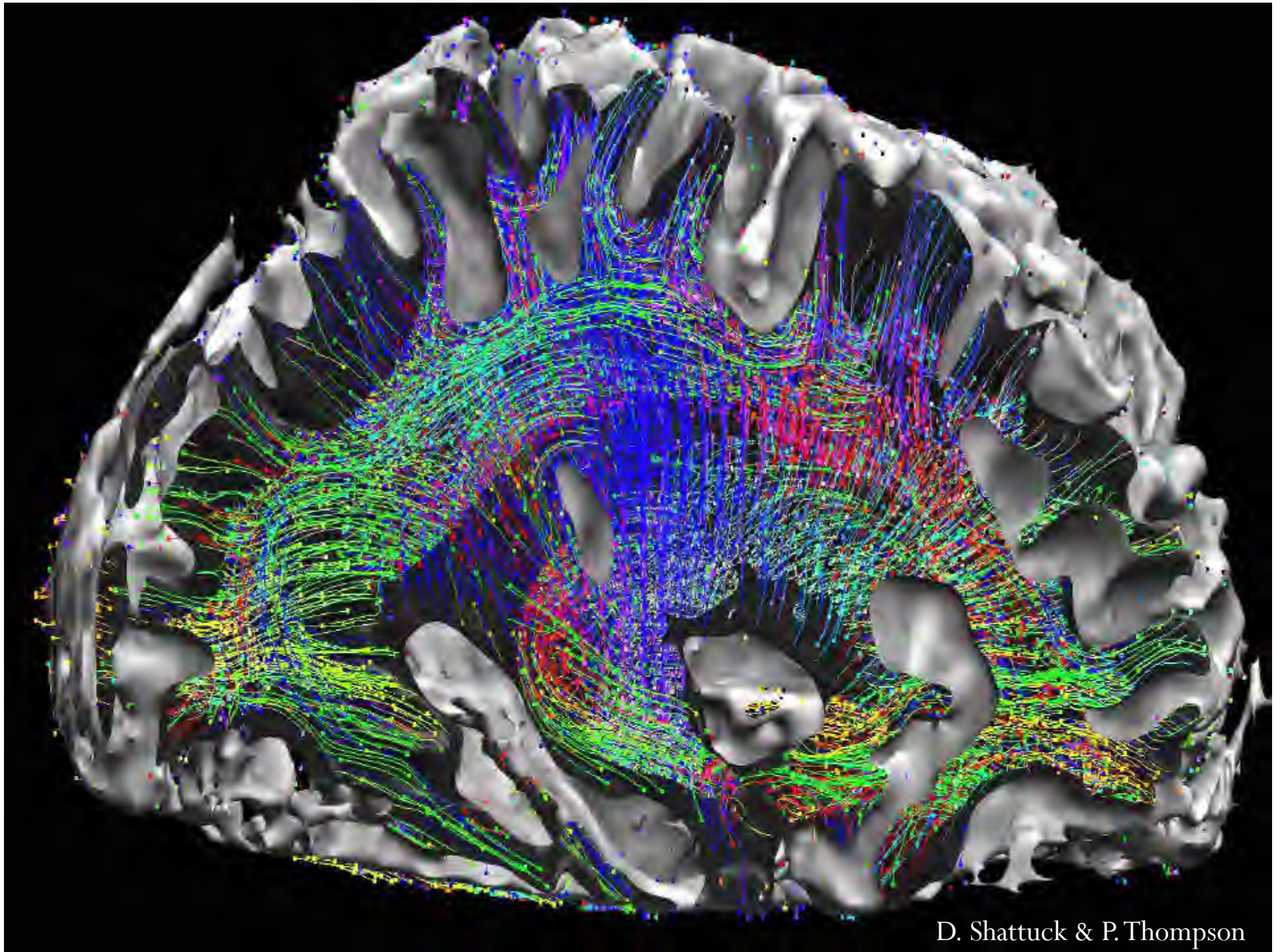




D. Shattuck & P. Thompson

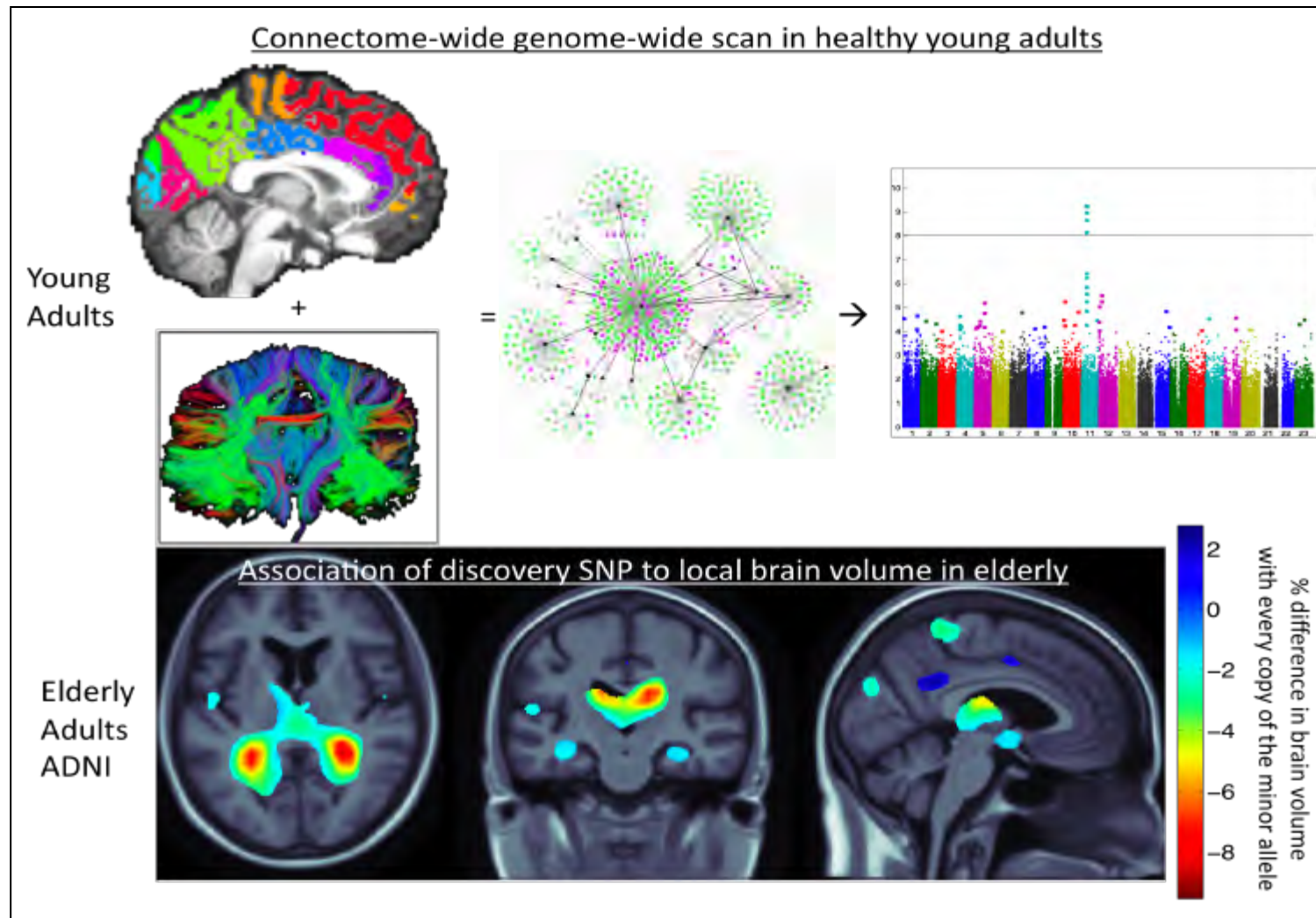


D. Shattuck & P. Thompson



D. Shattuck & P. Thompson

Genome-Wide Screen of the Human Connectome discovers an Alzheimer risk gene (ENIGMA-DTI)



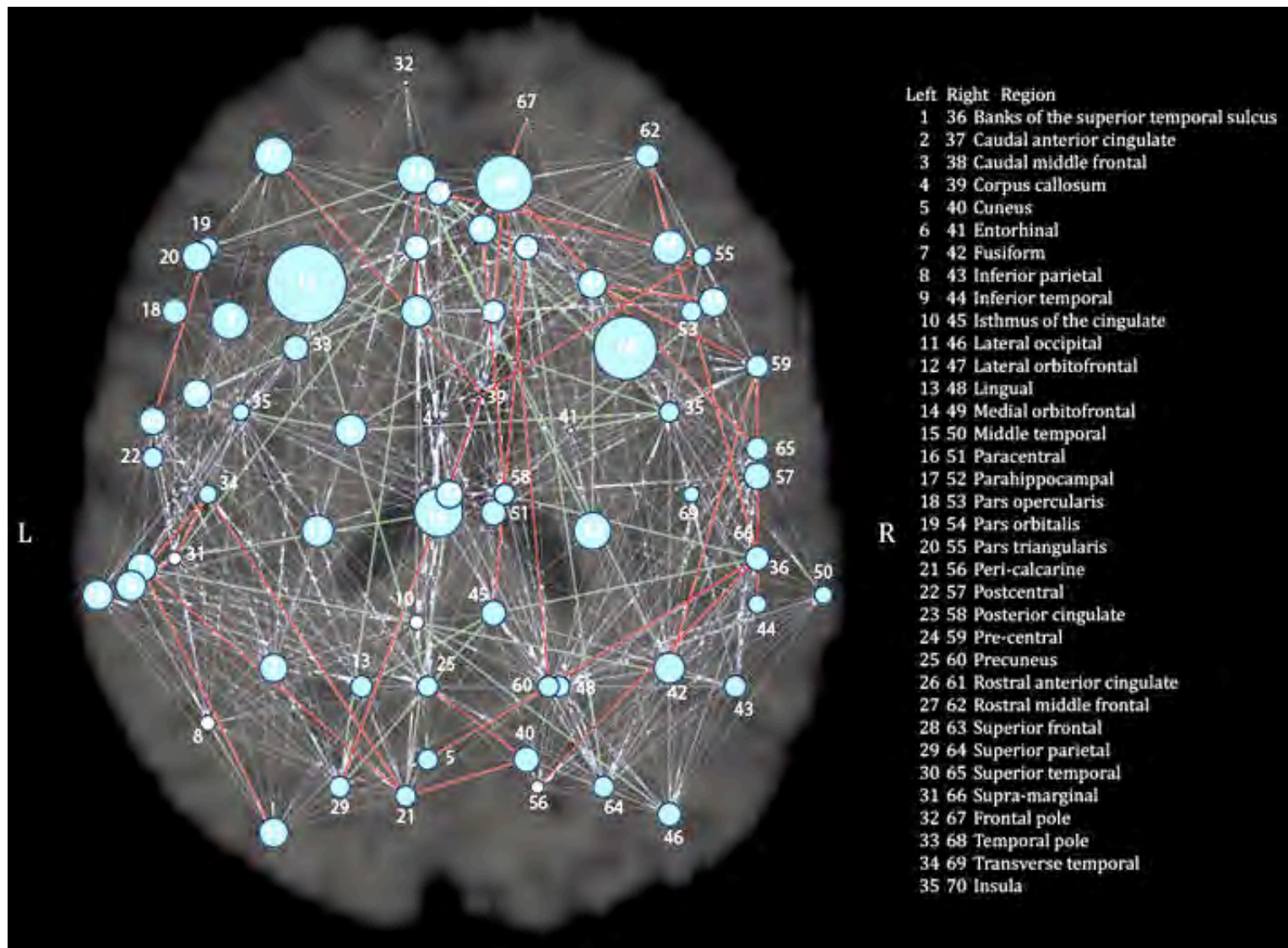
Discovery sample – Young Adults
Replication sample – ADNI

Jahanshad/Thompson, under review

Autism Risk Gene linked to Differences in Brain Wiring

CNTNAP2-CC Carriers have different networks

Circles show hubs with different eccentricity (a measure of isolation; N=328 people)



E. Dennis
et al., Brain
Connectivity,
2012

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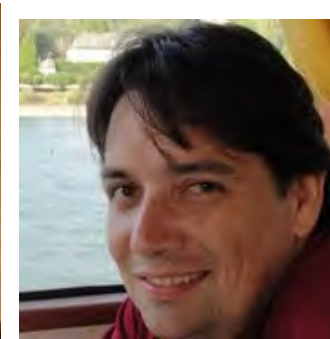
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207 co-authors and the 21,151* participants

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Working Groups:

ENIGMA1, ENIGMA2, ENIGMA-DTI,
ENIGMA-PIB, ENIGMA-PGC, ...

